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why? what? how?

Why do cancers of the prostate sometimes remain quiescent, to be discovered only at autopsy? *Why* do some cancers in situ of the uterine cervix become invasive, and others not? *Why* do some cancers of the breast and prostate respond to endocrine therapy, and others not; and *why* do they eventually become resistant to hormone therapy? *Why* do some leukemia patients respond to chemotherapy with some drugs and not with others; and *why* do they all eventually fail to respond to all the known antileukemics?

Why do some patients with cancer live five, ten, or twenty years, and others with apparently identical tumors die in a few months? *Why* does an occasional member of a multiple-intestinal-polypoid family remain well when all his siblings develop cancer of the colon? *Why* did about 100 cancer patients, authentically recorded in the literature, recover without treatment? *What* is the real nature of the protective mechanism against cancer, the tumor-retarding factors, or host resistance; is it

related to immune reactions against bacterial invasion? *What* effect has nutrition on cancer? *What* part do genes play in transmission of cancer? *What* cancers in man and animals are caused by viruses? *How* can epidemiological and statistical research aid in the control of cancer?

How do normal and malignant cells differ—physically, chemically, morphologically, and physiologically? *How* far do results of cancer research in animals apply to man? *Why* can certain types of cancer be induced in some species of animals and not in others? *What* are the secrets of growth, of differentiation, and of life itself? *How* can the results of all workers in cancer research be best utilized toward the ultimate control of cancer?

Answers to these and many other questions concerning the nature, cause, detection, diagnosis, treatment, prognosis, prevention, and cure of cancer are being sought by a host of research specialists in the basic and clinical sciences.

In the United States, this year, the public and private fund-granting agencies have available approximately thirty-eight million dollars for support of cancer research, and various institutions of higher learning are adding an amount difficult to determine. Modern technical know-hows implemented by such a sum must yield answers to many of the *whys* and *whats* of neoplastic disease, and eventually to the elusive *hows* of cancer control.

Cover—

The Cancer Puzzle—many newly developed instruments, apparatus, and techniques are being adapted to cancer research. The results of fundamental and applied physical, biochemical, and biological investigations are classified and evaluated. Each clean-cut, factual fragment, trimmed of its unproved edges, is matched and fitted into its proper place in the incredibly intricate mosaic of the cancer problem.



NEWSLETTER

MAY, 1957

Significant Developments In Basic Research -- (Continued from March issue)

Osgood (U. of Ore.) is "growing" and shipping to many research centers quantities of human leukemic cells. After eighteen years of semi-successful efforts to culture these cells, it occurred to him that oxygen tension might be the decisive factor. He inserted diagonally in his cultures a slide rule which permitted the cells to seek their own level. Growth became luxuriant.

Rieck (Marquette U.) has found that something in light repairs or prevents skin damage from overexposure to UV. Mice kept in darkness following three irradiations with UV had badly damaged skins, the epidermis becoming 10 times as thick as normal. Irradiated controls kept in light had little skin damage, with the epidermis only twice normal thickness.

Scientists have devised sensitive nephelometric and spectrophotometric techniques to determine quantitative and qualitative plasma-protein titers in humans. Antisera are produced by injecting chickens with specific human-plasma proteins. When human-plasma samples then are added to antisera, precipitation readings indicate how much of each protein is present. The work was done by Goodman, Ramsey, and Simpson of the Detroit Institute for Cancer Research and Remp, Basinski, and Brennan of the Henry Ford Hospital.

Carcinogens frequently enlarge the liver and inhibit body growth. Gutman, Filbin, and Peters (U. of Minn.) found that in 2-AAF-induced hepatoma the liver concentrates glycogen, lipids, and protein. Diets with 20-per-cent casein permitted normal rat-body growth but failed to effect liver enlargement. Dietary casein amounting to only 11 per cent had no effect.

Osdene and Taylor (Princeton) have developed a new chemical approach to the total synthesis of pteridines, and

their products will be tested against experimental tumors. Others have shown that this class of compound inhibits growth by antagonizing nucleic acid metabolism.

Landauer (U. of Conn.) in 1945 observed a mutant chick strain which he called "rumpless." It has become a goldmine of genetic errors. Mutations have been preserved and enhanced by breeding practices, mutagens, and carcinogens. Besides producing animals with no lower jaw, dwarfed or no beaks, single eyes, no ears, and no heads, the studies have led to good analyses of modifying genes which tend to offset mutation effects.

Brown and Gordon (Cornell and Sloan-Kettering) have found that a mushroom product identical with nebularine, a purine riboside, concentrates preferentially in fungi, embryonic cells, adult epithelium, fibroblasts, and one mouse tumor -- but apparently is inactive against three kinds of human cancer cells against which it has been tested. It acts upon the adenine and guanine phosphates.

Nishimura and Baum (Northwestern U.) have shown that bacterial polysaccharides and colchicine inhibit mitosis by blocking the gelling of protoplasm. Within 15 minutes after application of the drugs, cell viscosity drops from 33 to 50 per cent of normal values, although effects on cell division do not become apparent for five or six hours. Usually in less than 24 hours, drug effects wear off and cultures show the normal number of mitoses. The drugs appear to be effective only on dividing cells and those about to divide.

Au¹⁹⁹ for Bladder Cancer: Nelson of Richmond, Va., has treated eight cases of bladder cancer with radioactive gold. While the number of cases and elapsed time since operation are too little for definitive conclusions, the investigator feels that the isotope has wrought some good palliative effects in patients who lived long enough for observation (all were apparently beyond hope of cure by conventional means). The isotope proved lethal to tumor cells in injected areas and had a minimal effect on nearby stroma and structures. There was no evidence of generalized toxic reaction except in one patient who died of renal failure one month after the gold injection and after transplantation of both ureters. (Continued after page 108)

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Keeping up

Lung Cancer—Present Position

The authors summarize, with adequate documentation, the present state of knowledge concerning carcinoma of the lung—prevalence, etiology, pathology, diagnosis, treatment, and results of treatment. The phenomenal, and nearly universal, increase in prevalence of lung cancer over the years since 1933 has been referred to by Clemmesen (Copenhagen) as "the most striking and most important observation in the clinical field of cancer in our time." By 1950 bronchogenic carcinoma had become the most frequent cancer in men in the United States. The present rising incidence of total cancer in men seems attributable in large measure to primary cancer of the lung. Other environmental etiologic factors—radioactive materials (radium, uranium), asbestos, arsenicals, etc.—are almost forgotten in the present-day rush to establish excessive cigarette smoking as a possible etiologic factor. Condensed cigarette tar is carcinogenic for mouse epidermis. Primary carcinoma of the lung by definition includes all the epithelial malignant lesions arising in the bronchi or their accessory glands. The term bronchogenic carcinoma includes all entities except alveolar-cell carcinoma (bronchiolar carcinoma, pulmonary adenomatosis). Bronchial adenoma has certain malignant attributes—local extension and destruction, mitoses, and occasional lymph-node and liver metastases, but its clinical behavior and the possibility of cure by local excision exclude it from the true carcinomas of the lung. Carcinomas of the lung are classified as follows: epidermoid or squamous-cell carcinoma, adenocarcinoma, undifferentiated (large-

cell) carcinoma, oat-cell (small-cell) carcinoma, and alveolar-cell carcinoma. The oat-cell and the undifferentiated carcinomas are the most malignant and the most responsive to radiation. The squamous lesions yield best results from surgical extirpation and are less sensitive to radiation. The adenocarcinomas are quite radioresistant but offer a more favorable outlook when they can be removed. Knowledge of the pathology of the lesion is of therapeutic and prognostic value. The possibility of carcinoma of the lung must be considered in every man in middle life who presents otherwise unexplained cough, sputum, weight loss, chest pain, dyspnea, pneumonitis, wheeze, or hoarseness. Radiologic study is the most helpful single tool in diagnosis. Cytological studies of sputum and bronchial aspirates are useful. In the physical examination of the patient the supraclavicular and cervical lymph nodes are of utmost importance. The pathways of lymphatic spread are: carcinoma of the right lung may metastasize to the right intrapulmonic lymph nodes, the peribronchial nodes, and the paratracheal nodes; left lung lesions spread to the same nodes on the left side, and, in addition, those in the lower lobe drain via the subcarinal nodes to the paratracheal group of lymph nodes on the right side as well. Tissue-culture studies of pleural effusions by the "kinetic pathologic" method may reveal positive cells not otherwise demonstrable. Angiocardiography is useful in estimating the anatomic extent, and hence, the inoperability, of the lesion. The single case of regression of an untreated, histologically proved bronchogenic carcinoma makes interpretation of results of treatment difficult. Surgical extirpation is

with Cancer



the most effective means of cure. Pneumonectomy and lobectomy are standard procedures. "Radical" pneumonectomy includes intrapericardial ligation of the pulmonary artery and veins and dissection of the mediastinal lymph nodes. Survival is largely determined by the extent of the disease at the time of operation. The presence of positive nodes greatly diminishes the prospect of survival. The overall salvage rate in primary carcinoma of the lung is less than 10 per cent. Improvement of this figure awaits the results of surgery in the asymptomatic group and the effects of the extended types of operation. Surgery has attained nearly its limit in technical advance; further progress in the management and control of lung cancer is more likely to depend upon earlier diagnosis, preventive measures, and possible ultimate cure.

Wilkins, E. W., Jr., and Sweet, R. H.: Carcinoma of the lung. New England J. Med. 256:346-351, Feb. 21, 1957.

Irradiation or Surgery in Cervical Cancer

From an analysis of 231 cases of carcinoma of the cervix, 194 treated by irradiation, thirty-one by surgery, and six by both methods, it is concluded that radical surgery is not indicated for the primary treatment of invasive carcinoma of the cervix under ordinary conditions. Results of master surgeons under ideal conditions are in no way comparable to those obtained under average circumstances by ordinary radiation therapists. In the irradiated group there was no mortality due to treatment. In the surgical group no patient in whom the operative specimen showed

spread of cancer beyond the cervix proper survived, and operative complications were frequent. The overall five-year survival in the irradiated group was 26 per cent. The causes of failure of radiation therapy were: (1) inadequate dosage to the pelvic perimeter; (2) limitations imposed by dangers of injury to bladder, rectum, small intestine, and abdominal wall; (3) non-uniformity of dose within a given patient; (4) dose restrictions imposed by large volume of tissue irradiated; (5) ignorance of the actual extent of invasion; and (6) radiation-resistance of the tumor. The author is developing a method of utilizing irradiation together with surgery by removing the uterus and adnexa, and uniformly irradiating the entire potentially cancer-bearing areas of the pelvic floor by mould technique, with appropriate shields and displacement of the small intestines out of the pelvis during the irradiation period. Surgery, to offer a reasonable chance of cure, must be so extensive as to subject the patient to excessive risk of mortality and morbidity. In average hands, irradiation promises a great likelihood of cure with a considerably diminished risk.

Clayton, R. S., Sr.: Carcinoma of the cervix uteri: ten-year study with comparison of results of irradiation and radical surgery. Radiology 68:74-79, Jan., 1957.

Predeterminate Cancer

Cancers of the same site in different patients have marked differences in lethality. Cancer often behaves as a chronic disease, patients sometimes surviving ten or even twenty years. Cancer can no longer be considered as an autonomous, progressive growth since natural resistance

of the host to cancer has been demonstrated. The modern concept of the behavior of cancer is that its origin and growth depend on a balance of power between neoplastic and reactive influences in the host—termed by Macdonald "biological predeterminism." Therapeutic measures and prognosis should be based on more accurate criteria of the diverse biological potentialities rather than on duration and dimensions of neoplasia. More than 100 cases of spontaneous cures of diverse forms of human cancer have been reported. Autopsies reveal latent, unsuspected cancers of prostate, lung, kidney, and thyroid. Even the most rapidly growing tumors are dependent on factors, unknown at present, deprivation of which would lead to regression or latency. The histological and biochemical changes in the neoplasm cannot account fully for its behavior and course. Variation in the biological behavior of cancer is of far greater importance in determining survival than the speed of diagnosis or surgical intervention. Like all other tissues, cancer is subject to the unknown laws of age and death. Among the possible components of biological predeterminism in cancer are: (1) the intrinsic malignant potential of the tumor itself, (2) factors in the host and in the environment which would favor growth of the tumors, (3) tumor-retarding factors in the host. Patients with breast carcinomas commonly survive for less than five years if the tumor cells have markedly hyperchromatic nuclei, anisonucleosis, and numerous mitotic figures, and conversely those whose cancer cells are hypochromatic and all markedly similar almost always survive five years postoperatively. Cancers of the colon and stomach cannot be similarly graded prognostically. Biological aggressiveness of cancer types roughly parallels their degree of structural anaplasia. Survival has been shown to be inversely related to the heterologous transplantability of the tumor. Prognosis based on histological grading and transplantability is far from absolute accuracy. An example of tumor-trophic factor in the host is the increased lethality of breast cancer during pregnancy and lactation.

Certain breast and prostate cancers respond to the physiologic stimuli of castration and hormone therapy. Carcinoma in situ of the cervix may remain static for long periods before becoming invasive. Natural or strain resistance of the host to cancer has been demonstrated experimentally. Whether specific tumor antibodies are involved in human cancer cannot be decided from the available evidence. It is naive to assume that all cases of five-, ten-, and fifteen-year survival are the result of therapeutic intervention. When a tumor is beyond radiation or surgical extirpation and is quiescent and asymptomatic it is more reasonable to observe it than to attempt to treat it by means that at best would be only palliative. The forces that interact to produce the clinical picture of cancer lethality are extremely complex. More work is needed.

Black, M. M.; Speer, F. D., and Opler, S. R.: Some components of biologic predeterminism in cancer. Int. Abstr. Surg. 102:223-230, March, 1956.

GP and the Sigmoidoscope

The general practitioner has made a case for his routine use of the sigmoidoscope if he can say, "In the past few years I have prolonged the life of one man by diagnosing carcinoma of the bowel at a curable stage." Early cancer of the lower bowel is not painful and does not bleed. There may be only rectal discomfort and a little, persistent diarrhea. Inspection of the part with one's own eyes is the most certain method of examination and will reveal disease at an earlier stage and in a much wider area than digital examination. The straight metal tube, 30 cm. long, is equipped with a light that may be plugged into an auroscope battery. There is also a pump which can be used to inflate the bowel ahead of the advancing sigmoidoscope. A pair of long alligator forceps is used for swabbing areas of mucous membrane and for taking biopsy specimens. The only preparation of the patient that is required is that he should have defecated shortly before the examination. Purgatives and enemas are uncomfortable for the patient and disadvan-

tageous for the operator. If absolutely necessary, purgatives may be given two or three nights before the examination but never the night before. The patient must be in a true knee-chest position with the back arched toward the bed or table and the knees apart. After passing the resisting internal sphincter and the obturator has been withdrawn, the instrument advances by its own weight. Force must not be used. When no clear road is seen ahead the sigmoidoscope is withdrawn an inch or two and advanced again. The normal mucous membrane is smooth, glistening, and of a light pink color. In the lower rectum the submucous vessels cannot be seen, the color is darker, and the texture is granular. In the upper rectum and in the sigmoid colon the mucous membrane is paler and the submucous vessels can be seen. The sigmoidoscope is no less important to the general practitioner than the ophthalmoscope. Skill in the use of the instrument and training of the eye can be gained only by practice.

Hutchin, K. C.: Sigmoidoscopy in general practice. Proc. Roy. Soc. Med. 49:919-921, Nov., 1956.

Etiology of Cancer of Lung, Larynx, and Bladder

Figures for the total incidence of any form of cancer are of but little value; sex differences must always be considered. Although the incidence of lung cancer is about the same in non-smokers of both sexes, our present knowledge does not allow a forecast of the future incidence in women from the incidence trend in men. The carcinogens, 3,4-benzpyrene and arsenic, in polluted atmosphere may go beyond the respiratory tract and affect other parts of the body. The incidence of various forms of cancer is higher in urban areas. Various carcinogens, except ultraviolet, are more abundant in towns, and their actions may summate. In England and Wales the standard mortality rate for cancer of the lung for both sexes falls with decreasing urbanization, as does the rate for cancer of the larynx in males, but cancer of the larynx in women shows exactly the reverse relationship, possibly due to a

diet consisting too largely of white bread and tea. It is misleading to consider the simple summation of air pollutants and tobacco smoke in the etiology of lung cancer because the greater part of the former are filtered out in the nose. Negative results of smoke-inhalation experiments on animals are of no significance, because the animals, unlike smokers, keep their mouths shut and pass the smoke over their turbinates, which in many species are more complex than our own. Auerbach's recent finding of multiple foci of precancerous histologic changes in the bronchial tree suggests that "recurrences" following operation may actually be due to growth developing from another center of carcinoma in situ. Barmen, cellarmen, and licensed victuallers—concerned in the sale of alcoholic drinks are especially liable to cancer of the larynx. In England, the increased cost and decreased strength of alcoholic drinks since 1939 may be responsible for the fall in incidence of laryngeal cancer in men and for the change in its social incidence. Earlier the incidence was higher in the poorer classes; this gradient disappeared in 1950. Television might in time have a similar effect owing to lessened consumption of alcohol. The steady increase in cancer of the bladder in recent years in England and Wales and in Denmark requires an etiological search. The antidiuretic action of tobacco would facilitate any possible carcinogenic effect on the bladder of absorbed smoke constituents. Extracts of human urine injected subcutaneously into mice have caused fibrosarcoma. Search is now underway in urine of smokers and non-smokers for those carcinogenic compounds previously identified in cigarette smoke.

Kennaway, E.: Some questions on cancer of the lung, larynx, and urinary tract. Brit. M. J. 1:299-306, Feb. 9, 1957.

Breast Cancer

The majority of physicians and surgeons in this country favor the management of cancer of the breast by the Halsted radical mastectomy, others extend

this operation to include supraclavicular and internal mammary lymph-node dissections, and a few, here and abroad, favor less radical surgery, simple mastectomy, with more reliance on irradiation. At the New York Hospital the recommended treatment is radical mastectomy with axillary dissection and a large skin graft, and, when there is evidence of metastasis, roentgen irradiation to axillary, supraclavicular, internal mammary, and mediastinal lymph nodes. Radical breast amputation for cancer is as logical as removing a rotten apple from the barrel. We know that if it is allowed to remain it will extend and prove fatal. The first line of attack against this disease is in the patient's home, with periodic examinations of the breasts done by herself. The second line of attack is in the doctor's office, with routine periodic examinations of patients with breast symptoms. The third line of attack is the doctor who is able correctly to diagnose cancer in a patient presenting a lump in the breast. And the fourth line of attack is the hospital equipped for radical surgery, roentgen therapy, and endocrine therapy. The key to success in the management of cancer of the breast is early diagnosis, before incurable extensions have occurred. The alert physician will recommend prompt excision of any questionable lesion. Today 48 to 63 per cent of breast-cancer patients have axillary metastases when first seen. Twenty-five years ago the figure was 80 per cent. Of patients with breast tumors less than 3 cm. in diameter 24 per cent develop recurrences, and of those with tumors more than 5 cm. in diameter 40 per cent develop recurrences. And of those patients developing recurrences 90 per cent die within two years. Five-year survival is 62 per cent without axillary metastases, and 27 per cent with involvement of the axillary nodes. At ten years 41 per cent of the axillary negative and 19 per cent of the axillary positive patients are living. When the axillary nodes are not involved the patient's chance of doing well is doubled. The overall five-year-survival rate is at present 40 to 50 per cent. Approximately 37 per cent of patients have

metastases to the axilla. In one series 11 per cent of those without axillary nodes had involvement of the internal mammary chain. Radiation should therefore cover the axilla, the supraclavicular area, and the internal mammary chain with the branches penetrating into the mediastinum. Radiation is also useful in treatment of local recurrences and bone metastases, and in castration as the first step in endocrine palliative therapy. Hormone therapy helps more than 60 percent of patients so treated. Objective evidence of tumor regression occurs in 20 to 30 per cent of cases. Androgens are indicated in the younger patients and estrogens in those ten years beyond the menopause. Castration is an accepted therapeutic modality no less important now than before the advent of hormone therapy. Steroid therapy and bilateral adrenalectomy are useful in selected cases. Dr. Cooper detailed the diagnostic procedures of inspection and palpation of the breasts, referring also to the film by the American Cancer Society on "Self Examination of the Breast," and concluded that if all women routinely examined their own breasts at monthly intervals doctors would see more early cancer of the breast.

Cooper, W. A. (Moderator); Panel Members: Burnett, H. W.; Cohen, E. J.; Conway, J. H.; Hohman, C. W., and Stark, R.; Summary: Forkner, C. E.; Tumors of the Breast [A.M.A. Television Program]. New York Med. 12:242-251; 263-269, March 20, 1956.

Endocrine Therapy of Cancer

Hormonal control of cancer rests on the two principles that (1) cancer is not necessarily autonomous and intrinsically self-perpetuating, and (2) cancer can be sustained and propagated by a hormonal function at normal or even subnormal levels. Some neoplasms have the same functional reaction to hormones as their tissues of origin. Such tumors are termed hormone dependent. Physiologic studies of the prostate show it to be androgen dependent. Orchiectomy abolishes prostatic secretion and the prostate atrophies. Administration of phenolic estrogens similarly suppresses prostatic function. Administration of androgens, following or-

chiectomy or estrogen administration, restores secretion to normal. Neoplasms of the prostate developing in senility shrink after orchiectomy or estrogen administration, and are enlarged by androgen administration. The estrogen diethylstilbestrol, widely used in the treatment of prostatic carcinoma, was the first agent of known chemical composition, aside from radium, to ameliorate carcinomatosis—the beginning of the chemotherapy of cancer. Similarly, the breast and some cancers of that organ are under hormone control. Ovariectomy produces remissions, sometimes profound, in approximately 20 per cent of breast cancers. Marked beneficial effects have followed orchiectomy in cancer of the male breast. Testosterone causes regression of some breast cancers by an unknown mechanism. Other breast cancers, particularly in women past menopause, respond to administration of phenolic estrogens. Adrenalectomy for cancer of the breast, female and male, is based on the fact that the adrenal cortex secretes enough hormones to maintain hormone-dependent tumors after castration. Still more profound atrophy of hormone-dependent organs and their tumors in animals results from hypophysectomy. When applied to therapy of breast cancer, remissions are obtained in some cases, even after castration and adrenalectomy have lost their effects. Radiation hypophysectomy with the cyclotron proton beam has obtained decrease in function of the target organs, but the effects in breast cancer are not yet certain. In acute and chronic leukemia and in Hodgkin's disease, ACTH and cortisone yield remissions of varying duration. In about 50 per cent of children with acute leukemia, these agents induce profound remissions, but only of a few weeks or months.

Huggins, C.: *Control of cancers of man by endocrinologic methods; a review. Cancer Research. 16: 825-830, Oct., 1956.*

Management of Advanced Cancer

In a case of advanced malignant disease the decision concerning the possibility of cure is usually easy since the only hope

for cure lies in total extirpation of the neoplasm. Once cure has been abandoned, attention is directed toward prolongation of life and the comfort of the patient. Radiation, which must be left to the experts, can often relieve pain or reduce pressure by shrinking the tumor, and, in some cases, as in cervical carcinoma, may even give permanent cure. Transplanted cancer cells, metastases, are unusually sensitive to radiation. Bone pain from metastases often responds to radiation. Even cerebral metastases, if single, may respond; brain tissue is fairly tolerant to radiation, although its blood vessels are not. Neoplasms sensitive to radiation are generally sensitive to chemotherapeutic agents. Chemical agents include (1) the antimitotics—nitrogen mustard, triethylenemelamine, triethylenethiophosphoramide, myleran, and Fowler's solution, and (2) the antimetabolic agents—the two folic acid antagonists (aminopterin, amethopterin), and the two purine antagonists (mercaptopurine and urethane). Cortisone and ACTH are valuable both by specific, direct effect on the tumor cells and by reducing the undesirable reactions to other chemotherapeutic agents. These chemical compounds are most widely used in the leukemias and lymphomas. Myleran in chronic myelogenous leukemia seems to hold out hope of actual lengthening of life. Among the surgical procedures useful in advanced cancer are: removal of liver metastases found at removal of bowel carcinoma; removal of solitary metastasis to the lung, especially from the thyroid or kidney; the "second-look" operation for possible recurrence after removal of colon or stomach cancer; relief of pain by rhizotomy, chordotomy, and leukotomy; and orchiectomy, ovariectomy, adrenalectomy, and hypophysectomy. All of the doctor's medical skill and human kindness is needed for the management of these patients, who often depend solely upon him for a word of comfort and to listen to the day's complaints. He should remember that some day he himself will go down the same trail.

Copping, G. A.: *The management of advanced malignancy. Canad. M. A. J. 76:319-322, Feb. 15, 1957.*



a glance . . .

**one-minute abstracts
of the current literature
on cancer research . . .**

Cancer Research in U.S.A.

Great discoveries often come from observing the significance of some unexpected finding that turns up in the pursuit of some apparently commonplace inquiry. It is, therefore, advantageous that the inspired investigator actually do his own laboratory work, rather than direct it by assignment to technicians and junior assistants who may not recognize the most important side results. The necessity for team work in the increasingly complex technologies brings many problems in co-ordination. Some medical team scientists have no biological training and are baffled by the vagaries of living patients and their diseases. In this country strong pleas must be made for fundamental as opposed to applied research, since the latter has more immediate appeal to the laity, who in one way or another must foot the bill. The public sometimes specifies the use to be made of its contributions—cancer, psychiatry, poliomyelitis, and does not always give most generously to the most necessary purpose. Some organizations financing research look for immediate practical returns, but others with wider, long-term vision even help promising men to enter the research field and see them through the non-productive years. In America medical research is done in university medical schools and allied institutes, under

various foundations, some with their own institutes, in self-supporting clinics, in the chemical and pharmaceutical industries, and with the support of scientific societies and voluntary health organizations. The pattern of research is also influenced through direction and support by the government—local, state, and federal. Direct governmental interference in research has led to many notable advances, but there is danger in control of research by politicians. In spite of the inequalities and difficulties of integration, medical research proceeds in an immense productive flood.

Raydin, I. S.: The strategy of medical research. [Editorial.] Surgery 41:328-329, Feb., 1957.

Cancer Research in Great Britain

Cancer research may be said to have begun when Pott in 1775 attributed scrotal cancer of chimney-sweeps to contamination of the skin by soot. Over the next century many classical contributions were made by Hunter, Hodgkin, Paget, and others. In 1902 the laboratories of the Imperial Cancer Research Fund were founded under the aegis of the Royal College of Physicians of London and the Royal College of Surgeons of England. Among the researches proceeding in these laboratories today are: survival of tumor cells with special reference to "paramorphisms," mammary cancer, fowl leu-

kosis, and endocrine and azo-dye carcinogenesis. The Fund later provided a clinicopathological laboratory at Lincoln's Inn Fields where a study of urinary mammotrophism is now being made. In 1909 the Research Institute of the Royal Cancer Hospital was founded. It was here that the basic work on amino acids and vitamins was done. Later attention has been given to carcinogenesis. This Institute together with the Physics and Radiotherapy Departments of the hospital in 1939 was redesignated the Chester Beatty Research Institute, and is now a school of the University of London maintained mainly through the Medical Research Council. The British Empire Cancer Campaign, inaugurated in 1923, currently distributes support to research upon almost every aspect of cancer: carcinogenic properties of mineral oils, mechanism of carcinogenic action, alkylating agents as carcinogens and mutagens, vesical implantation of carcinogens, carcinogenic hydrocarbons, carcinogenesis by ionizing radiations, statistical and field studies of the association of lung cancer with the cigarette habit and with air pollutants, intimate chemistry of the cancer cell, structure of DNA and the action upon it of the alkylating carcinogens, nucleic acids of tumors, hexosemonophosphate oxidative pathway of carbohydrate metabolism, excretion of steroids, tryptophan and β -glucuronidase metabolism in bladder cancer, tumor viruses, tumor immunology, relationships to malignant disease of familial intestinal polyposis and of chronic ulcerative colitis, therapy of chronic myelogenous leukemia with myleran, of malignant melanomas with chlorambucil, and of neuroblastoma with vitamin B₁₂. The study of experimental chemotherapy is on a smaller scale than in the United States. American agencies sponsoring cancer research in British laboratories include the U. S. Public Health Service, the Jane Coffin Childs Memorial Fund for Medical Research and the Anna Fuller Fund. The Seventh International Cancer Congress will be held in London July 6-12, 1958.

Haddow, A.: *Cancer research in the United Kingdom*. [Guest Editorial.] *Cancer Research* 16:821-824, Oct., 1956.

Cancer Research in Japan

Two years ago cancer mortality in Japan surpassed that of tuberculosis, increasing public concern with the cancer problem. The Government is now planning to augment research funds and to strengthen the cancer sections of the national hospitals which have been the successful bases in the tuberculosis campaign. The need for treatment facilities is considered to be more urgent than for those for research. At present only two institutions are devoted to cancer research: The Cancer Institute, of the Japanese Foundation for Cancer Research, with its attached Koraku Hospital, the only cancer hospital in the country and founded by Nagayo in 1934, and the Sasaki Institute, started as Sasaki's private laboratory for biochemical research. In addition to these institutions, the medical schools and universities contribute part-time research from their pathology, biochemistry, and clinical departments. The only journal on cancer research is *Gann*, established in 1907 by Yamagiwa, who with Ichikawa first reported tar cancer of the ear of rabbits. The leaders in cancer research—Nagayo, Ogata, and Fujinami—are pathologists. There is a general interest in carcinogenesis—for example, the production of subcutaneous sarcomas in rats by various dyes at the Cancer Institute, Tokyo, and the dye-induced hepatoma by Sasaki and Yoshida. Several types of ascites sarcoma of rats have been maintained in various institutes, and in 1951 new interest was aroused by the ascites hepatoma, a reproducible ascites tumor of epithelial origin. The author reveals his secret mental blueprint of a chain of international cancer hospitals, supported by an international organization, where patients regardless of the country in which they live would have an equal opportunity to obtain the best treatment available. Each chain hospital would encourage the establishment and improvement of other cancer hospitals, and would supply a useful basis for international geographic surveys of cancer.

Yoshida, T.: *Cancer research in Japan*. [Guest Editorial.] *Cancer Research* 16:1007-1008, Dec., 1956.

Developments in Cancer Research

There is no one cancer problem. Its many problems include causation, nature of the malignant state, diagnosis, treatment, epidemiology, and the metabolic consequences of cancerous growth. Cancer research is often thought of as only that proceeding in the laboratory, but epidemiological and clinical research is of no less importance. The ideal solution of the problems of cancer would be its prevention, but this is impossible without better knowledge of its causation. Only a small part of total cancer research is concerned with this important aspect. Genetics, physiologic and biochemical, is another promising, young field in cancer research. Epidemiological methods are being adapted to systematic study of cancer as it occurs in racial, geographic, occupational, and other groups. Only six clearly identifiable agents are known to cause cancer in man: (1) roentgen rays and the related radioactive substances, (2) ultraviolet radiations, (3) arsenic, (4) β -naphthylamine, (5) benzidine, (6) 4-aminodiphenyl. Many other substances, essentially mixtures, have been incriminated in the production of cancers in man: soots, shale oils, paraffins, nickel and chromate compounds, and isopropanol. Benzpyrene is carcinogenic for mice and was probably the causative factor in chimney-sweep's cancer described by Pott. Tobacco smoking and atmospheric pollution have been shown to increase the risk of lung cancer. Carcinogenic agents may act at sites distant from their portal of entry to the body. The virus hypothesis of the production of cancer is now an active field of cancer research. There is steady progress in producing neoplasms in mammals by filterable agents obtained from cancers. The milk agent of Bittner has many of the attributes of a virus. Lymphomatosis in chickens is caused by a filterable agent. Latent infection with carcinogenic viruses may be widespread. The species specificity of carcinogenic viruses now known poses serious difficulties in studying the viral etiology of cancer in man, for which no evidence exists today. Regardless of what

agents may be capable of inducing malignancy, the immediate cause of cancer must be the production of a self-propagating, heritable abnormality within the cell. Mapping of the chromosomes and their genes in relation to predictable risk of developing specific types of experimental cancer is proceeding. Curability of cancer depends more upon its anatomic extent than upon its size. Cancers responding to chemotherapy usually become refractory, much like susceptible infective organisms to antibodies. Chemotherapeutic research clearly contributes to our basic knowledge of cancer. Cervical carcinoma in situ offers opportunity to study the tissue and cell changes leading to malignancy. Biologic and biochemical attributes of cancer cells deserve closer attention in refining diagnosis and prognosis. Further study of cancer-cell seeding of operative wounds would improve surgical prognosis. No all-inclusive diagnostic screening test for malignant neoplasms is yet available. Variations between cancer and normal cells in respect to chemical and biological attributes are being studied intensively—biochemistry, enzyme chemistry, metabolic pathways, chromosomes, deoxyribose nucleic acids, etc. Much is being learned of the nature of the cancer cell from study of the leukemias and their therapy by chemical agents. The search for a drug as potent in cancer as is penicillin in certain infections should be continued.

Mider, G. B.: Some developments in cancer research. J. Chron. Dis. 4:296-320, Sept., 1956.

Results of Cancer Research

One of the most extensive scientific efforts in medical history is now being made against cancer. Advances are being made on all fronts of research related to this effort. Cure rates are increasing for cancers of the breast, uterus, stomach, and for certain cancers of the head and neck. Palliative measures—particularly chemotherapeutic—have improved the outlook for the patient with advanced cancer. Great improvement has been made in the treatment of leukemia. Gains in survival

have been made largely in the localized, external, and accessible cancers; the disseminated and less accessible remain beyond the effective reach of available therapy. Today one cancer in four receiving proper treatment is cured. One more of the four could be cured if all known advantages were utilized—early detection, prompt surgical and radiation therapy. The other two must await the advances of future research—laboratory and clinical. Laboratory studies include problems related to carcinogenesis, the nature of the cancer cell, and tumor-host relationships. There are many examples of fundamental scientific studies in other fields that have found application in the study of cancer. The whole subject of exfoliative cytological diagnosis of cancer evolved from studies in basic sciences of cytology and morphology. The radioactive isotopes used in cancer research, diagnosis, and treatment are by-products of developments in atomic energy. Clinical cancer research includes the search for better methods of diagnosis and treatment—surgical, radiation, and chemical. Remarkable refinements and improvements have been made in cancer surgery. Adrenalectomy and other palliative procedures have been devised for use when direct attack on the tumor is impossible. New techniques and more effective standardization of dosages have increased the value of radiation therapy, including the isotopes. But the most notable clinical advances have been made in chemotherapy, including hormones, particularly in the palliative treatment of inoperable cancers and the leukemias. Although the problems in cancer research remaining unsolved are serious and complex, we have reason to believe that the present intensified cooperative effort will lead to their solution.

Heller, J. R.: *New horizons in cancer research. Connecticut M. J.* 19:823-826, Oct., 1955.

Team Research and the Individual

Progress in cancer research parallels that of science in general. Hypotheses, theories, and tenets of today can be evaluated only with the passage of time, since

discovery of new evidence may change the status of a formula. They can be tested only by individuals. New ideas, new approaches, and new methods must come from individual minds. Emphasis on the team approach to research may be salutary if the position of the individual is clearly recognized. Any effective group must have a leader, whose personal qualities, intellectual capacity, and technical competence are such that others seek his guidance to further their own development and identify their own research objectives with his. There is no single way of organizing cancer research, which must be a composite of individualistic enterprise. Leaders are the keys to success. Mere scientific competence is readily available but leaders have never been abundant in any society. The future of cancer research rests heavily on better means of encouraging the efforts of the intellectually curious, technically skilled, highly imaginative, and sincerely interested—the uncommon man.

Mider, G. B.: *The uncommon man. [Editorial.] Cancer Research* 16:469-470, July, 1956.

Clinical Cancer Research

In the past few years the internist has joined the surgeon, the radiologist, and the pathologist in their investigations in the field of cancer. A major area of cancer research is chemotherapy—the search for drugs which selectively destroy or control the growth of cancer cells. For intelligent participation in chemotherapeutic research the internist requires a detailed knowledge of the natural course of each of the major forms of cancer and of the results of conventional methods of therapy, particularly in patients with inoperable or far-advanced disease. He has for study and treatment the many physiological disturbances that may occur in the cancer patient—nutritional, hepatic, renal, cardiac, electrolyte, endocrine, pulmonary, neurologic, infectious, and psychiatric. The patient himself, if properly briefed, is often willing, or even eager to participate in clinical research. The testing of more and more new drugs is desirable to detect

even the slightest favorable response, pointing the way to more effective compounds. New drugs must be evaluated practically and their therapeutic indications determined for various forms of cancer, in different stages of the disease, and in comparison with other methods of treatment. Radiotherapy is the most widely used technique in the palliative treatment of cancer and the internist should know its indications, dosages, hazards, and results, and should cooperate with the radiologist in investigating the applications of ionizing radiations, including the radioactive isotopes. Many observations made under the aegis of cancer research have wider applicability to other areas of medical research. For example, the work on nucleic acid metabolism may be applicable to the treatment of virus diseases, and to the basic understanding and even control of genetic factors in man. From the turmoil and controversy characteristic of research emerges a basic knowledge of the disease to which every pathologist, radiologist, surgeon, internist, biochemist, and biologist concerned with cancer can contribute.

Karnofsky, D. A., and Rawson, R. W.: *Symposium on the medical aspects of cancer; introduction.* [Editorial.] *M. Clin. North America* 40:575-579, May, 1956.

Cancer Registers in Research

Cancer registers, unlike many registers for other diseases, play a role in research because they record the fate of all diagnosed cases regardless of the nature of the treatment or of whether any service is rendered to the patient or his family. The hospital cancer register can be used in the evaluation of therapy since it includes all cases. State central cancer registers are valuable in computation of incidence and prevalence rates. Well-run central cancer registers, useful for research, are expensive. Total annual cost for a state register is in the neighborhood of two million dollars. In addition to case registers, fruitful work in cancer epidemiology requires analyses of mortality data, retrospective studies of diagnosed cases and matched controls, long-term observations of special

groups, morbidity surveys, and application of screening tests. All these diverse approaches are used in, and supported by, the National Cancer Institute. There is a need for additional states in different regions of the country to sponsor cancer registers oriented to research so that findings may be collated and examined for consistency or for evidence of divergent state or regional patterns. The specialized personnel for these registers—physicians trained in epidemiology and statistics—is deficient and should be increased by supplementary financial and technical support including training groups.

Heller, J. R.: *Cancer registers.* [Editorial.] *J. Chron. Dis.* 4:644-645, Dec., 1956.

Problems of Cancer Research

Cancer initially is a disease of the individual cell and differs from other diseases in that it is not essential to have something from outside the organism taking part in the disease process, at least in the early stages. Later other processes—infection, degeneration, etc.—come in to give the characteristic symptoms of cancer. Although the cause of cancer is not understood, we know many ways in which cancer can be induced—experimentally and in human beings. This knowledge has come largely through clinical observations of industrial hazards. At the end of the last century Moreau made the first successful transfer of a tumor from one mouse to another and observed that tumors of the subcutaneous tissues and adenocarcinoma of the breast were not uncommon in the female mouse of his colony. Some of his grafted tumors appeared at other than the transfer sites, and daughters of mice with such tumors often developed similar tumors, suggesting a hereditary factor. In 1936, Bittner showed this apparent hereditary transmission of tumors to be the result of a factor in the milk now generally considered to be a virus. Ellerman and Bang, in Denmark in 1908, showed leukemia in fowls to be transmissible from one animal to another by cell-free extracts. Later, Rous and Murphy in America, and Fujinami, in

Japan, working with spontaneous fowl tumors, reported the first clear-cut examples of experimental transmission of tumors by tissue extracts free from tumor cells. The author has shown that chicken tumors can readily be induced by injection of certain chemical substances, and that these tumors are transmissible not by cell-free extracts, but only by grafting. He also showed that radon irradiation of any site in birds bearing recently induced "virus" sarcoma would provoke local tumor growth in the reaction zone. In the human, primary tumors do not commonly occur in sites remote from the site of irradiation reaction, suggesting that it is unlikely that most human tumors are virus-induced. The first pure substance to be identified as carcinogenic was 3,4-benzpyrene in soot. It induces tumors in rats, mice, and most of the animals in which it has been tested, but not so far in monkeys. Nothing short of a deliberate experiment would establish its activity for the human subject. Hundreds of pure chemical substances have since been shown to be carcinogenic for various animals, and a few of these chemicals are human cancer hazards. One of the most versatile carcinogens yet found is 2-acetylaminofluorene, designed as an insecticide but not marketed because it induces a great variety of tumors in almost every species of animal. Some of the azo dyes used in many industries and in the coloring of foods are carcinogenic. One of the most difficult problems of cancer research is the increasing use of synthetic chemicals in industry. Reaction of body cells to these newly encountered substances is unpredictable. Elaborate systems of experimental control are necessary to safeguard against the possible carcinogenic substances. The most careful experiments with animals will not indicate safety or danger for the human subject. We have no means of telling whether we are more like rats, mice, dogs, or monkeys in our chemical reactions. Certainly they should not be added deliberately and unnecessarily to human foods.

Peacock, P. R.: *Some problems of cancer research. Radiography* 21:231-233, Nov., 1955.

Research in Chronic Diseases

There has been greatly increased financial support for research in the chronic diseases in recent years. The emphasis has been on laboratory and clinical research. Epidemiology, primarily a public-health method of investigation, has been relatively neglected in the study of chronic diseases. Laboratory and clinical research will eventually elucidate the mechanisms of many of the chronic diseases, and advances in therapeutic management give promise of better control of these diseases by stopping them or delaying their progression before disability and incapacity result. Public-health investigators have the responsibility of studying the problem and of contributing their skills to the prevention and control of these diseases, and the support and rehabilitation of those affected. With particular reference to cancer, the author mentions the early mass detection of lung cancer by roentgenographic screening, and of cervical cancer by mass cytological screening as was carried out so effectively in Memphis, Tenn. It is unfortunate that the technical difficulties of obtaining specimens from cancers of other sites make similar mass cytologic screening prohibitive.

Multiphasic screening for cancer can be successful in cancer detection centers, and when meshed with the normal flow of patients through medical channels, such as physicians' offices, outpatient departments, hospitals, and industrial medical examinations. The object of these screening procedures is to bring the disease under management in an incipient or asymptomatic stage rather than in the symptomatic stage when diagnosis is usually made.

Dunn, J. E.: *Public health research in chronic disease. Pub. Health Rep.* 71:67-74, Jan., 1956.

Fifty Years of Cancer Research

The trigger mechanism which led to a great expansion of cancer research was the discovery in 1904 that mice that had recovered spontaneously were immune to subsequent transplants of the same tumor strain. Even Ehrlich, who had previously

said that more reputations had been ruined in the field of cancer research than in any other, began to experiment with transplantable mouse tumors. Fluctuations in the development of immune reactions and of tolerance suggested an antagonism between the tumor and the host. Results of these early experiments suffered from the lack of pure-strain mice. Nevertheless, they stimulated interest in cancer research. Today every field of research bearing directly or indirectly on cancer is being thoroughly explored. The greatest contrast between cancer research of today and of fifty years ago is in the freedom now granted to research workers in choosing a field of investigation and deciding what courses to follow. Annual expenditure on cancer research was about one-thousandth of what it is today. The leaders were university and medical school professors who worked on cancer in their spare time. There were very few full-time investigators, and it was impossible to embark on any large-scale, long-term experiments because of the uncertainty of continued financial support. Now the numerous research laboratories devoted to cancer research have the most up-to-date facilities and equipment, and are manned by able investigators who cooperate in an effort to bridge the gaps between their respective fields. Whereas fifty years ago there was little or no incentive to engage in cancer research, today, the results being obtained in the field are so important and the opportunities for research are so excellent that able young investigators need have no hesitation about engaging even in long-term projects in this most difficult and fascinating field of research.

Clowes, G. H. A.: *Cancer research fifty years ago and now.* [Editorial.] *Cancer Research* 16:2-4, Jan., 1956.

Clinical Cancer Research

We need in the cancer field many more workers — cloistered, academic, fundamental, and unhurried, on whom no demands for practical results should be made, but from whom, in time, we hope for some increase in understanding from

whatever unlikely direction their inquiry may have led them. A plea is made for more middlemen between the fundamental and the clinical investigator. Such a middleman must be familiar with the whole subject of cancer. He must find his way into research laboratories and staff rooms, to talk, to listen, to attend meetings, and to read review articles. He must engage in research on his own account—in the hospital ward and in his own experimental laboratory. He selects, sorts, and analyzes the detailed clinical observations. He develops ideas which he passes to the basic research workers to test hypotheses formed from clinical application of their work. To this middleman, any special intracellular evil—mutation, virus, special disorder of nucleic acid metabolism, or any other agent which increases cellular activity or damages control mechanisms—may at times be responsible for disorganized growth. The causes of cancer are those many conditions which lead to physiological isolation of cells from their fellows in any complicated organism. These multiple causes may either raise cell activity above its control or lower the controls. The first group includes most of the irritant, inciting, carcinogenic factors, all those injuries which demand repeated attempts at regeneration, recurrent local hormone stimulation, and any intracellular changes which may increase cellular growth potential. The second group of causes contains the poorly understood process of ageing, those nervous and metabolic gradients which largely determine and maintain our growth and form, perhaps some of the cancer-promoting agents which may affect these local control mechanisms, and the general hormone system of diffusible control of homologous disease and of tissues related in some common function throughout the body. Hope for the future lies in more efficient prevention or postponement of tissue disorganization, in better removal or destruction of some disorganized tissues, and in renewed attempts at re-establishment of control. Many investigators have become so fundamental that they appear to be looking for a cause of something which

seems to be life, and for a cure of something which seems to be the second law of thermodynamics. Achievements in cancer research have been great. They are underrated because they have supplied no simple solutions to the questions of cause and cure. There is no single solution, no specific intracellular evil, and no universal cure.

Smithers, D. W.: Clinical cancer research. Lancet 1:253-257, Feb. 11, 1956.

Basic Biological Research

Research not only adds to our knowledge but also supplies an understanding and insight into the interrelationships of knowledge. Science formerly was a means of getting to know the world; now it is enlisted to change the world. It is a disservice to unify where no unity exists by trying to explain phenomena of different natures on a single basis. Hypothesis must not be confused with proof. Conflicting hypotheses and doctrines stimulate investigation to determine truth. Distraction from the primary purpose or objective of research often causes great inefficiency. The eye must be kept on the target. Even the most precise data are meaningless unless they are directly related to the phenomena under investigation. Basic problems of biological research are the forces that control cell growth and reproduction, and particularly those forces that stop this growth and reproduction when the organism is complete. The underlying mechanism and causes of differentiation and of hereditary transmission of parental traits are of fundamental biologic importance. Early medicine was based on a consideration of the whole individual. Later individual organs, and still later, parts of organs, and then tissues were scrutinized from the standpoints of function and morphology—normal and abnormal. After thousands of years of this slow progress Virchow focused attention on the cell as the basic unit. Today we are looking at cytoplasmic constituents and at parts of nuclei, Mitochondria, chromosomes, and chemical constituents of cells are being studied. We have only recently come to

regard cells as analogous to molecules. Just as in and within the atom there lies a whole new world of structure and force of infinite importance, so it is with the components of the cell. Broad vistas lie before the investigating biologist and biochemist, and they are contained within the cell—even within the parts we now toy with as an infant toys with his rattle.

Hopps, H. C.: On the philosophy of research. Texas Rep. Biol. & Med. 14:362-371, Fall, 1956.

Statistical Cancer Research

Cancer case registers are important tools of cancer research. The experimental method has been applied to human populations in the therapeutic field for some time past but only recently in the field of carcinogenesis. The methods used in the statistical approach to the study of cancer are: (1) analyses of mortality data, (2) retrospective studies of diagnosed cases and matched controls, (3) forward studies of defined cohorts, (4) morbidity studies, (5) screening of populations for precursive signs, and (6) case register operations. Recently concern has greatly increased with epidemiological investigations of lung cancer. Offices of vital statistics contain much basic information on the distribution of cancer mortality by age, sex, race, and other demographic variables, but mortality data alone cannot answer questions concerning survival experience among specific categories. The retrospective technique is being applied to studies of occupational factors, and, with the expanding use of vaginal cytology, will be employed more frequently in future studies of carcinoma *in situ* and invasive carcinoma of the cervix. In the forward study technique a group of individuals (cohort) is selected as of a fixed point in time. They are then classified with regard to certain characteristics, and followed forward in time to determine their fate. This approach can be applied to industrial carcinogens, and was recently used in correlating cigarette smoking with lung cancer. Morbidity surveys—in hospitals and among physicians—yield more reliable results on incidence (cases diag-

nosed for the first time in the survey period) than on prevalence (the total number of persons with cancer). Morbidity surveys are concerned with diagnosed cases. Extension of this approach includes population screening for undiagnosed and precancerous cases. The use of vaginal cytology to detect unsuspected carcinoma in situ or invasive uterine cancer is a current example of population screening. Lesions found in community chest surveys are followed for their possible neoplastic significance. The recent impetus given to cancer registers by the American College of Surgeons has resulted in the maintenance of cancer registers in many hospitals, as well as central registers in city, county, and state health departments. Central registers depend on their sources of information, not the reverse. The more general, and the more coordinated, cancer registers become the more progress can be made in statistical cancer research.

Haenszel, W., and Hon, N. B.: Statistical approaches to the study of cancer with particular reference to case registers. J. Chron. Dis. 4:589-599, Dec., 1956.

Experimental Design

Medical knowledge advances by a combination of many different kinds of observation—controlled and uncontrolled—some directly and some only tangentially relevant to the problem at hand. This is illustrated by the various types of evidence concerning the relation between the use of tobacco and lung cancer, such as animal experiments, and retrospective and prospective studies. A long planning phase is usually necessary before embarking on any experiment. The objectives of the experiment, consisting of a series of questions to be answered or hypotheses to be tested, must be clearly formulated. There is always the danger of trying to answer too many questions with one experiment; none may be answered satisfactorily. The pre-experimental plan should include a consideration of the way the results are going to be reported—what tables are to be compiled and how the data are to be analyzed. The usual way of

increasing the accuracy of experiments is to increase the number of subjects utilized. When subjective measurements are involved the observer must guard against changing his scale of measurement or criteria from one group to another. Control groups must be chosen with care toward close correspondence with the test group except for the phenomenon under investigation. Bias of the observer and of the observed is obviated by the well-known blindfold techniques.

Fertig, J. W.: Design of medical experiments. Texas Rep. Biol. & Med. 13:758-767, Winter, 1955.

Epidemiologic Cancer Research

The classical principles of epidemiology as applied to communicable disease may be applied to a great variety of other disorders, conditions, and situations, including cancer. Epidemiology considers all factors and interrelationships that affect the occurrence and course of a disease in a population. These factors include the characteristics of the host population; the causative agencies—predisposing, precipitating, and perpetuating; and the biological, physical, and social environment. Descriptive epidemiology considers the incidence and prevalence of a disease in time, place, and group. Epidemiology as a method is an orderly scientific approach to the collection and analysis of data having to do with causation and behavior of disease. The epidemiologist working with reported mortality from cancer must evaluate and explain its fluctuations in consideration of all known facts, and move cautiously in attributing increase or decrease to mere changes in classification. The influence of a very large number of factors in cancer causation could be estimated epidemiologically by taking advantage of the enormous differences in race, diet, environment, customs, occupations, etc., in human populations. To obtain fully reliable results in research work on a demographical basis, absolute, uniform, international methods of registration and nomenclature are vital.

Macdonald, F. J.: Epidemiology of cancer. Texas Rep. Biol. & Med. 13:826-839, Winter, 1955.

Cancer Research in the United States

O. Malcolm Ray, Ph.D., and Ralph G. Meader, Ph.D.

The purpose of this article is to review for practicing physicians recent developments in cancer research. Space does not permit a detailed discussion of any of the many aspects of the general problem nor does it allow acknowledgement of the many investigators whose work will be mentioned. Inasmuch as neither of the authors has been engaged in investigative work for some years, it is to be understood that they take no credit for the progress that is reported here.

Studies of carcinogenesis, the causes and mechanisms involved in converting normal cells into cancer cells, continue to go forward on many fronts. By implanting small pieces and films of a large number of commercial and highly purified plastics and synthetic resins in various locations within laboratory animals, it was found that appreciable numbers of tumors developed in most cases. Invariably the tumors were located adjacent to the plastic material. Similar studies with metal foils of silver, tin, tantalum, vitallium, and stainless steel induced some cancers with all metals except tin. The injection into mice of large doses of four different polymeric chemicals known as polyvinylpyrrolidones (PVP), which have been used as plasma expanders occasionally, induced cancers of the lymphoid tissues, uterus, skin, ovary, and breast. For the most part, the cancers developed at the sites where the PVP was retained. Although there is little direct evidence that these types of materials will induce cancer in man, this possibility should be kept in mind in deciding upon the use of surgical techniques which involve leaving plastics or metals in the body permanently.

Compounds highly carcinogenic for animals have been extracted from many environmental materials including tobacco

smoke, fuel combustion products, dye intermediates, coal tar and related substances. One investigation has shown that when several different strains of rats were fed a dye (4-dimethylaminoazobenzene), certain strains developed many more liver tumors than others. In those strains which were susceptible to cancer induction, the dye was very firmly bound to some protein in the liver cells whereas this did not occur in the other strains. Thus, whether cancer developed, depended upon the type of protein in the liver cells which in turn depended upon the genetic constitution of the animal. Another study still in progress has shown that a similar situation exists in the case of a quite unrelated carcinogen (N-2-fluorenylacetamide) which produces tumors of the liver, breast, and auditory canal in rats. Ten urinary metabolites of this compound have been identified. It is still not clear whether the compound itself or one or more of its metabolites combines with the liver proteins to induce the cancers.

Whole-body roentgen irradiation of mice induces lymphatic leukemia unless the thymus gland is removed after the irradiation. If, however, the irradiated thymus is replaced by transplanted normal thymus tissue, the increased incidence of cancer is partially restored. Thus, the induction of cancer requires the presence of the thymus and is not simply due to the irradiation of the thymus.

Practically 100 per cent of irradiated young female mice will ultimately develop ovarian tumors. In this case, however, the tumors will not develop if the irradiated ovaries are replaced by transplanted normal ovaries. One explanation for this phenomenon is that irradiation reduces the ability of the ovary to produce estrogens. In an effort to stimulate the function of the ovary, the pituitary produces excessive
(Continued on Page 92)

From the Research Grants Branch, National Cancer Institute, Bethesda, Maryland.

C CURE
 ++ MARKED INHIBITION
 + MODERATE INHIBITION
 ± QUESTIONABLE ACTIVITY
 - NO ACTIVITY

ACTIVITY OF COMPOUNDS AGAINST

	NITROGEN MUSTARDS ANETHOPTERIN HYDROCORTISONE N-METHYLFORMAMIDE N-METHYLACETAMIDE 6-MERCAPTOPURINE URETHANE METHYLCARBAMATE CHLORAMPHENICOL POTASSIUM ARSENITE 8-AZAGUANINE												8-AZ
SARCOMA 180	+	++	±	++	-	C	+	-	-	-	-	-	-
FLEXNER-JOBLING	C	-	±	±	-	++	+	-	-	-	+	-	-
WALKER 256	C	-	+	±	±	+	+	-	-	-	-	-	-
MAMMARY CA. E0771	±	-	+	±	-	++	+	-	-	-	+	-	-
SARCOMA T241	-	-	±	-	±	±	-	-	-	-	±	-	-
GARCINOMA 1025	C	-	+	+	+	++	±	-	-	-	±	-	-
MECCA LYMPHOSARCOMA	-	++	±	±	+	-	-	-	-	-	±	-	-
MAMMARY CA. RC	-	-	-	+	-	C	-	-	-	-	-	-	-
"SPONT." MAMMARY CA.	+	±	++	-	-	+	±	-	-	±	±	-	-
MAMMARY CA. 755	±	-	+	++	+	C	+	-	-	±	++	-	-
BROWN-PEARCE	±	-	-	-	+	+	-	-	-	±	+	-	-
GLIOMA 26	-	-	-	-	-	++	±	-	-	-	-	-	-
LEUKEMIA L1210-S	±	+	-	+	-	+	-	-	-	-	+	-	-
EHRlich ASCITES EF	++	+	-	+	-	±	±	-	-	±	-	-	-
EHRlich ASCITES ELD	+	±	-	±	-	-	-	-	-	±	±	-	-

*The table shows the activity of compounds against experimental tumors in rats and mice. Most of the data are derived from a survey sponsored by the American Cancer Society to examine the methodology for selection of antitumor compounds. (Gellhorn, A., and Hirschberg, E., Eds.: Investigation of diverse systems for cancer chemotherapy screening. Cancer Research Suppl. No. 3, 1955.)

AINST EXPERIMENTAL NEOPLASMS *

	8-AZAXANTHINE	BENZIMIDAZOLE	D-GLUCOSAMINE	2,6-DIAMINOPURINE	MYLERAN	STILBESTEROL	2,4-DIAMINO-5-(3,4'-DICHLORO-PHENYL)-6-ETHYLPYRIMIDINE	DARAPRIM	1,5-DIAMINOBIURET	D,L-ETHIONINE	β-2-THIENYLALANINE	DESOXYPYRIDOXINE	COLCHICINE	5-METHOXYTOLUQUINONE	NETROPSIN	AZASERINE
1	-	-	-	-	-	+	+	±	-	-	-	-	-	-	++	
2	-	-	-	-	±	±	-	-	-	-	-	-	-	-	+	
3	-	-	-	±	-	+	-	-	-	-	-	-	-	±	+	
4	-	±	-	±	+	±	-	-	-	-	-	-	-	-	-	
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
6	-	±	-	±	±	±	-	-	±	-	-	-	-	±	-	
7	-	-	-	-	-	-	±	-	±	-	-	-	-	+	+	
8	-	-	-	-	-	±	-	-	±	-	-	-	-	-	±	
9	-	-	-	-	±	±	±	-	-	-	-	-	-	±	±	
10	-	-	-	+	±	±	±	-	+	-	-	+	±	-	±	
11	-	-	-	-	+	±	±	-	+	-	-	-	-	-	±	
12	-	-	-	-	+	-	-	±	+	-	-	+	±	-	-	
13	-	-	-	-	+	±	-	-	+	-	-	-	-	-	-	
14	-	-	-	-	-	-	±	±	-	-	-	-	-	-	±	
15	-	-	-	±	-	±	-	±	-	-	-	++	-	-	-	
16	-	-	-	±	-	-	-	-	-	-	-	+	-	-	-	

The term Cure is used when, following drug therapy, there has been complete regression of some of the experimental tumors with no evidence of recurrence in three months. For convenience, the shortest available name of a compound is used, and activities of a variety of mustards are included under the heading, Nitrogen Mustards.
 Tabulation provided by Dr. L. D. Hamilton, Sloan-Kettering Institute for Cancer Research, New York, New York.

amounts of gonadotropic hormone which induces cancer in the irradiated ovary. Implantation of the normal ovary restores the hormonal balance.

Sub-microscopic particles which appear to be viruses have been shown to play a role in the induction of sarcoma and leukemia in chickens, skin tumors in rabbits, mammary tumors in mice, and kidney tumors in frogs. A few years ago it was reported that leukemia could be transmitted to very young mice a few hours after birth by the injection of a cell-free filtrate from leukemic mice. New evidence has been obtained that this same material will also induce parotid tumors and sarcomas in mice. In chickens also it seems that a single agent or a combination of very similar agents will induce three different types of tumors. Recently a virus has been reported which consistently induces leukemia in mice regardless of age and sex and much more rapidly than heretofore. There is practically no direct evidence of the relation of viruses to cancer in man. However, because viruses are related to so many tumors in animals, and because man is known to carry some and perhaps hundreds of latent viruses, it would be surprising indeed if viruses play no role in human cancer.

Studies of the characteristics of a cancer cell, the differences between cancer and normal cells, and the relation of the cancer to its host are of perhaps less interest here and are mentioned only in passing. Their importance should not be underestimated. In fact, the successful detection and treatment of cancer may depend on the demonstration of critical differences between normal and cancer cells. For example, a recent report suggests that only cancer cells can absorb complete protein molecules. This raises the possibility of destroying cancer by the injection of proteins combined with radioactive elements or other toxic substances. If the presence of a virus is essential for the maintenance of the cancerous state, it may ultimately be possible to develop antibodies or vaccines that will affect only cancer cells.

A number of new methods and techniques are being applied to the detection and diagnosis of cancer. The first application of the exfoliative-cytology test as a mass-screening procedure for the detection of early uterine cancer was begun about four years ago. The first examination of 108,000 women led to the discovery of about 800 cases of cancer, equally divided between early cervical cancer and advanced uterine cancer. Ninety per cent of the early cancers and 30 per cent of the advanced cancers were entirely unsuspected. A second examination of 33,000 women led to the diagnosis of seventy-two early and eleven advanced cancers. The decreased incidence of advanced cancer in the second examination indicates the usefulness of this mass-screening procedure.

Continuing efforts are being made to utilize this same test by obtaining cells from early cancer in the stomach, lungs, bronchial tree, bladder, colon, and other organs. Basically, the problem is to develop an instrument or a method of washing which will recover cells from early cancers in these areas. A recent report indicates that in the case of the stomach, simply washing it with saline solution is less damaging and more useful than several mechanical methods that were tried.

Several laboratories are investigating the use of ultrasonic radiations, which are reflected like radar, in detecting cancer. This approach seems to have promise in tumors of the liver, breast, and other soft tissues. Instruments have been developed which convert the reflected ultrasonic waves into visual images.

Numerous efforts are being made to find or devise a dye or a radioactive compound which will be selectively absorbed by some cancers and can thus be used for detection purposes. As yet, however, these methods are of only limited help in detecting early cancer. There are no reliable general chemical or "blood" tests for cancer. Acid phosphatase determinations in prostate cancer and certain steroid metabolite analyses in some endocrine cancers may be useful diagnostic aids.

Surgery and radiation remain the two most effective means for treating cancer and they are only palliative for disseminated cancer. In surgery the importance of improvements in pre- and postoperative care should not be overlooked. They make possible the radical surgery frequently necessary for cancer of the lung, of major portions of the liver and digestive tract, and of the bladder or of sex organs from which the cancer may have spread to adjacent organs in the pelvic region.

In the case of radiations, the conventional roentgen rays and the use of radium or its substitutes such as radioactive cesium or cobalt, are still the treatments of choice in general and can cure localized and accessible cancers. Beneficial palliative effects may be obtained even in generalized and disseminated cancer in some cases. New techniques are being devised to make better use of these methods. Fine needles or nylon tubes containing radium or its substitutes may be inserted around or threaded through a cancer and may be removed after the proper exposure is obtained. Rotational therapy has been developed in which the patient or the radiation source rotates in such a way that the roentgen rays are continually focused on a cancer within the body. Because of the rotation, the skin and superficial tissues receive much less radiation than the cancer on which the beam is focused.

High energy radiations may be obtained from radioactive materials like the cobalt "bomb," or they may be produced mechanically. Their production involves accelerating a stream of electrons to extremely great speeds by applying a high voltage. When a beam of these electrons is directed against an appropriate metallic target, high energy roentgen rays are produced. A billion-volt linear accelerator of this type occupies most of a large building. However, a six-million-volt "midget" model which produces high energy roentgen rays at the rate of 600 roentgens per minute is in use. The beam can be focused on the deepest tissues of the body and yet is less damaging to the intervening tissues than the "softer" roentgen rays.

Supervoltage instruments can be adapted to use the electron beam directly for therapy. The electrons or "beta particles" are more readily captured by tissue than the roentgen rays or the "gamma rays" from radium, so it may be easier to control the localization of their effects. Supervoltage therapy is easier to plan and produces less systemic reaction. It has not been effective against cancer which is resistant to conventional therapy and it is dangerous in the hands of the uninitiated. It will not perform miracles but, where wisely used, it can be expected to improve, slightly at least, the ability to cure certain selected cancers and to aid materially in the alleviation of suffering. It will by no means supplant conventional roentgen-ray therapy or radium.

Continuing efforts are being made to induce cancers to take up radioactive compounds selectively and destroy themselves. The classical example of this is the uptake of radioactive iodine by the thyroid gland. Bone and breast tumors take up appreciable amounts of radioactive phosphorus. Attempts are being made to attach radioactive elements to compounds that are selectively absorbed by specific tissues and to treat cancer cells so they will absorb radioactive compounds that will not penetrate normal cells.

A great deal of emphasis is being put on chemotherapy, the use of chemicals, which is probably the most promising approach to the treatment of disseminated or metastatic cancer. Before a compound can be tried in cancer patients, it must be found or synthesized, it must be tested for growth inhibiting activity on tumors in animals and on other biological systems, and finally, the safe and maximum doses must be determined through studies of its pharmacology and toxicity in animals.

During the past year more than 12,000 compounds have been obtained for testing against cancer in animals, principally mice. It is anticipated that this number will increase to approximately 35,000 during this year. These compounds consist primarily of synthetic organic chemicals and antibiotic filtrates of various micro-

biological organisms. That increase in production of compounds has necessitated an equivalent increase in facilities for testing them against tumors in animals. It is considered desirable to test each compound against at least three different types of tumors in inbred mice. Up to ten mice may be required for a single test. Thus, during the coming year it is estimated that a million inbred mice will be required for use in 100,000 tests. Steps already have been taken to increase the production of inbred mice from the present level of approximately 250,000 a year.

The evaluation of the effectiveness of a chemotherapeutic compound in cancer patients is an expensive and time consuming process. Even the largest research center can carry out such a study on only a comparatively few patients over a period of many months. To resolve this difficulty a number of clinical investigators are now forming cooperative research groups of five to ten individuals from several institutions. They draw up jointly a protocol which they all use so that the same types of cancer are treated with the same compounds in exactly the same way. By this means the effectiveness of various compounds may be compared and the data on a large number of patients from several institutions may be combined.

Already the list of compounds which have some place in the treatment of one or another type of disseminated cancer is a long one and includes estrogens, androgens, ACTH, cortisone, P^{32} , I^{131} , thiouracil, urethane, thiotepa, TEPA, TEM, nitrogen mustards, myleran, amethopterin, aminopterin, prednisone, chlorambucil, 6-mercaptopurine, and azaserine. Each of these compounds has produced useful palliative effects or prolonged remissions against some type of cancer. Ultimately, however, the cancer becomes resistant. Nevertheless the use of these compounds in patients and animals has contributed information about the way they work and suggestions for the synthesis of related compounds that may be more effective.

In the meantime, new results continually appear. Amphenone may provide an effective substitute for the surgical re-

moval of the adrenal glands which is sometimes necessary in certain types of cancer. Using methotrexate, it has been possible for the first time to produce marked regression of a malignant solid tumor (choriocarcinoma) in patients. A derivative of quinoline, 4-(para-diethylamino-styryl) quinoline dihydrochloride, caused complete remission of lymphomas in 300 rats within five to twelve days. Another compound, 4-aminopyrazolo (3,4-d) pyrimidine, destroyed several types of cancer cells but had no effect on normal cells.

A discussion of cancer therapy would not be complete without mention of the use of oncolytic viruses. The normally occurring APC (adeno-pharyngeal-conjunctival) viruses have a dramatic, destructive effect on uterine carcinoma in patients although the cancer cells become immune and the cancer recurs. Several neurotropic "exotic" viruses, originally obtained from Africa, destroy human cancer tissues grown in tissue culture, in embryonated eggs, and in rats. Some of these show promise of clinical application. The use of oncolytic viruses is a particularly encouraging possibility because viruses in general are so specific for certain types of cells and because the activity of these viruses can be attenuated or modified so readily.

That the cancer research effort has not been in vain is indicated by a recent report on the five-year-survival rate of some 75,000 cancer patients covering a period of nearly twenty years. In this period the five-year-survival rate for all cancer patients combined rose from 19 per cent to 25 per cent for males and from 29 per cent to 38 per cent for females.

Several crucial questions remain unanswered. How does a normal cell become malignant? What are the critical differences between normal and cancer cells? Why do cancer cells ultimately become resistant to the effects of radiations, hormones, and chemicals? The answers to these questions will come from the highly important fundamental investigations barely referred to in this article and will make possible a truly rational and informed approach to the cancer problem.

KINESCOPE 28:
HORMONAL AND CHEMICAL TREATMENT OF CANCER

This kinescope is available through your Division of the American Cancer Society.
Running time: 52 minutes; 16-mm. color with sound.

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In this program the rationale of treating cancer of the breast, cancer of the prostate, and lymphomatous disease by altering hormonal balance is discussed. Objective methods of evaluating the effects of castration, adrenalectomy, or various steroids on metastatic bone disease from cancer of the breast and prostate are included. The results of hormonal treatment in the above and other types of tumors are also presented.

APPROVED FOR INFORMAL STUDY CREDIT BY THE
AMERICAN ACADEMY OF GENERAL PRACTICE

References to Cancer Research in Previous Issues of CA

1:181, Sept., 1951	Value of genetics for early diagnosis of cancer.
1:186, Sept., 1951	Electron-microscope examinations of human milk.
5:Cover, Mar., 1955	Roswell Park Memorial Institute.
5:Cover, May, 1955	The Institute for Cancer Research and The Lankenau Hospital Research Institute.
5:159, Sept., 1955	Cancer chemotherapy and the structure of DNA.
6:160, Sept., 1956	Current lung-cancer research in the United States.
6:169, Sept., 1956	Current status of lung-cancer research; some pathogenetic aspects.
6:190, Nov., 1956	Exfoliative cytology in research and diagnosis.

Semantics of Synergism

It would be better if in chemotherapy the word "potentiation" were always used for a degree of synergism which is greater than additive, while "synergism" or "synergy" were used as a broad term, covering all forms of "working together" from potentiation to merely partial addition.

Collier, H. O. J.: Discussion on synergy in chemotherapy. Proc. Roy. Soc. Med. 49:880, Nov., 1956.

The evidence that led to the passing of legislation concerning benzol, aniline and a host of other dangerous industrial solvents is of exactly the same type as that which incriminates cigarette smoking as a factor in the genesis of carcinoma of the bronchus.

Anon.: Lung cancer. [Commentary.] Brit. J. Clin. Pract. 11:80, Jan., 1957.

The Father of Chemotherapy Speaks

"I have wasted fifteen years of my life in that way [experimental cancer]. Until some fundamental discovery has solved the mystery of life itself, our knowledge of cancer will not advance a single step."—Paul Ehrlich.

The Virus Etiology of Cancer

Wendell M. Stanley, Ph.D.

The first clearly recognized tumor to be transmitted from animal to animal in series by means of a cell-free filtrate was a sarcoma that appeared spontaneously in a Plymouth Rock chicken. This extremely important observation was made by Rous in 1911 and the Rous sarcoma virus has been the subject of many investigations which have continued to this day with much profit. Since 1911 other viruses causing cancers in chickens, pheasants, ducks, and other fowls as well as viruses causing tumors in mice, frogs, rabbits, deer, and other animals have been discovered.^{1-3, 5, 6, 8, 13, 15-17, 20, 24, 25} Evidence for the virus etiology of cancer has come from so many different laboratories and has been of such good quality and quantity that I find it very difficult to understand why so many investigators have continued to have such a firm blind spot with respect to the virus causation of cancer. However, during the past few years there does seem to have been a definite change in the attitude with respect to the relationships between viruses and cancer. Many investigators accept viruses as etiological agents for animal cancers but are unwilling to consider them of etiological importance in cancers of man. The fact that only two, little studied and benign virus-induced tumors of man are known and that viruses have not yet been seriously implicated in human cancer does not mean that they are not there and that they are not of etiological importance. Basic biological phenomena generally do not differ strikingly as one goes from one species to another. Recent advances in the cultivation of human cells in vitro and especially in the newer knowledge of certain properties of viruses warrant today a marked change in our thinking on the problem of human cancer. The time has come when we should assume that viruses are respon-

sible for most, if not all, kinds of cancer, including cancer in man, and design and execute our experiments accordingly. Acceptance of the viral etiology of human cancer as a working hypothesis will involve a marked change in attitude on the part of many investigators. Acceptance of this idea may yield experimental results of the greatest benefit to mankind.

Since there is no evidence that human cancer is infectious, many investigators believe that because viruses are infectious agents they cannot possibly be of etiological importance in human cancer. However, this is not a valid conclusion because it is well known that viruses may be highly specific, so specific in fact that a given virus will infect and cause disease only in one kind of cell in one kind of animal. The Rous sarcoma virus when first isolated would cause cancer only in blood relatives of the chicken from which it was obtained. Later on this virus was adapted to other chickens and to other types of fowl such as ducks and pheasants. There would be little expectation that a virus long adapted to existence in human cells would grow readily in most animal cells. However, the fact that human viruses have been found to grow in certain animal cells indicates that the situation is not completely hopeless and hence that the search should continue. It should be obvious that great difficulties might be involved in demonstrating the existence of a virus actually present in a human cancer. The techniques that have proved useful in demonstrating the existence of certain animal cancer viruses have not yet been used in experiments with human cancer. Until these techniques have been used exhaustively without success it would be foolish to disregard the role which viruses may be playing in human cancer. The cultivation of human cells in vitro opens up wonderful experimental possibilities. We have in our own

From the Virus Laboratory, University of California, Berkeley, California.

laboratory about a dozen different kinds of normal and malignant cells of human origin under cultivation. While most of these are being used for studies on the effect of known viruses, it is obvious that such cells can be examined for the presence of hitherto unknown as well as known viruses or can be used as test materials for suspected human viruses. Significant new findings may be expected to result from this new and potentially extremely powerful experimental approach.

Another fact of importance, first recognized with the Rous sarcoma virus, is that a given tumor may be transmissible for a time only by the inoculation of living cells and later be transmissible by means of cell-free filtrates. It was thought that the variation in transmissibility was due to differences in the amount of virus produced. The amount of virus present in the tumor tissue is dependent upon the age of the host⁹ and the age of the tumor;⁴ in general the younger the host and the younger the tumor the more virus that can be extracted. The rate of virus production within cells may vary greatly. Changes in nutrient or in temperature during the period of virus growth can cause drastic changes in the amount of a virus present in a host. Before one concludes that a given tumor is non-viral in nature, one should be certain that the extract has been tested on cells known to be susceptible and to yield a demonstrable reaction with the virus and that the virus is absent in fact and not just present in provocative yet sub-infectious amounts.

One sometimes hears the argument that cancer viruses do not exist in human beings because if they did exist someone would have found them by this time. Some attention might have been given to this argument some years ago, but not now, for literally dozens of hitherto unknown human viruses have been discovered during the past year or so. We have today many more human viruses than we know what to do with, hence there is now certainly no reason to shy away from giving consideration to viruses as causative agents in cancer for the lack of viruses.

The fact that infection of certain can-

cer cells with certain viruses causes the destruction of the cancer cells is most significant. Because of the well known plasticity of viruses it should be possible by means of already known passage techniques to develop viruses having no effect on normal cells but with a special predilection for the destruction of cancer cells. Several laboratories are already engaged in work of this type.

It has long been known that cancer could result from prolonged exposure to coal tar and since 1920 extensive studies on chemical carcinogens have been made. These have been divided into locally acting and remotely acting carcinogens with the former causing cancer at the site of application and the latter causing tumors in specific organs or tissues regardless of the site or manner of application. It has generally been assumed that the carcinogen has caused some change in a cell which then progresses to cancer, but a few investigators have suggested that the chemical carcinogen works by activating or by causing a mutation in a latent virus. Duran-Reynals⁷ found that in practically every case treatment of chicks, adult chickens, and pigeons with methylcholanthrene activated a latent fowl pox virus, which produced lesions which progressed to cancer. His work certainly brings to the forefront the question as to whether fowl pox is a potential cancer virus.

In view of the great variety of carcinogens which range from hundreds of different kinds of chemicals, to physical agents such as ultraviolet or roentgen radiation and to mechanical effects such as continued abrasions or irritations, the supposition that cancer results from some change within the cell is quite reasonable. But if cells have viruses as passengers within them and viruses can cause cancer, it is just as reasonable to assume that these diverse agents are affecting the virus as it is to assume that they are affecting the genetic apparatus of the cell.

Viruses may persist within the cells of man for years, if not for a lifetime. Most human beings acquire the virus of herpes simplex quite early in life and, in many, the evidence for the persistence of this

virus throughout their lifetime is quite good. Psittacosis virus can persist in the form of an inapparent infection in groups of parrots and certain other birds for long periods of time only to have frank disease appear following unusually crowded conditions.²¹ The persistence of a virus in man for many years, for a lifetime, or even for two or more generations should not be regarded as an unexpected or unusual phenomenon but rather in complete accord with a well established biological principle.

Man has coursing through his body many viruses which were unknown a few years ago and we do not know what many of these are doing there. Viruses can persist in their hosts for generations in either an infectious or a non-infectious form, they can mutate to form new strains that cause different disease symptoms, and they have different effects depending on the age, genetics, and state of nutrition and hormonal balance of the host. Different carcinogenic agents can activate latent viruses with consequent cellular destruction. And viruses can cause cancer. It is difficult to escape the conclusion that viruses may be the etiological agents for most, if not all, cancer, including cancer in man, and that this represents by far the most intellectually satisfying working hypothesis which is consistent with all presently known facts. Of the greatest importance is the fact that acceptance of viruses as etiological agents in cancer generally will stimulate new experimental approaches to the cancer problem which have been long neglected and which are only now getting started in several laboratories.

The fact that the activity of the mouse mammary carcinoma virus is affected by the age, genetic composition, and state of hormonal balance of the host and that virus imbibed by an infant can insure mammary cancer in old age are most significant. Information gained in studies²² on one of the fowl-lymphomatosis viruses has made possible a much more intelligent approach in studies on the possible virus etiology of human leukemia. Certain viruses represent the most potent and most

rapidly acting carcinogenic agents known.

An important discovery from our laboratory has to do with the nature of a virus inside a cell. It has been known for some time that a bacterial virus infects a cell by attachment to the cell wall followed by the transfer of the deoxyribonucleic acid from inside the virus to inside the cell.¹⁸ It has not been known whether this is a general phenomenon and no one had ever demonstrated that nucleic acid alone possessed virus activity. Recently in our laboratory Fraenkel-Conrat and Williams separated tobacco mosaic virus into its protein and ribonucleic acid components and then reconstituted active tobacco mosaic virus from the several hundred constituent components. Subsequently Fraenkel-Conrat¹¹ made mixed viruses by combining the nucleic acid from one strain with the protein component of another strain and found that the nucleic acid determined the resultant disease. He also made the important discovery that it was possible to prepare nucleic acid possessing virus activity. Gierer and Schramm, working independently, reported a few days later that they had obtained nucleic acid possessing virus activity. This work is in line with the earlier results with the deoxyribonucleic acid of bacterial viruses and proves for the first time that virus activity can reside in a ribonucleic acid molecule. This means that a ribonucleic acid molecule on entering a cell can direct the course of intracellular events so that not only is it replicated but a characteristic protein is produced with which the nucleic acid eventually combines for its own preservation. Nucleic acids of cells deserve much closer attention than they have been given in the past. Skipper, following studies on nucleic acid metabolism in animal neoplasms, concluded that certain of the heterogeneous groups of agents which affect neoplastic growth also affect chemical events involved in nucleotide metabolism and hence that different approaches to the cancer problem seem to be leading to the nucleic acids.

It is now necessary to revise the generally accepted definition of a virus to include nucleic acids and perhaps also to

include replicating structures which do not evidence infectivity in the usual sense because normally they are duplicated only once or a minimal number of times during each cell division and never leave the cell. Such a viral nucleic acid might appear to be a part of, or associated with, the genetic apparatus of the cell but be subject to chemical or physical stimulation or shock which could cause it to mature, increase greatly its rate of replication, perhaps mutate, but in any case to separate and act as an independent functional unit. In order to differentiate such a replicating structure from the normal components of the cell it is imperative that initially the structure or virus must have entered the cell from without.

Knight and Beard and associates¹⁰ have found purified preparations of influenza and of erythromyeloblastic leukemia viruses to retain antigenic components characteristic of the host in which the virus

was grown. In time it may prove possible to separate active nucleic acids from these preparations, and, if so, on the basis of our findings with tobacco mosaic virus, this complication will disappear.

The recent findings in the virus field indicate more and more that the virus problem and the cancer problem are one and the same. The experimental evidence now available is consistent with the idea that viruses are the etiological agents of most, if not all, cancer, including cancer in man. Acceptance of this idea as a working hypothesis is urged because it will result in the doing of experiments that might otherwise be left undone, experiments that could result in the solving of this great problem. The past few years have seen the development of important new knowledge and of especially powerful new tools, and if we take full advantage of these we could easily tip the scale towards the solution of the cancer problem.

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CANCER CLINICS



Research in Occupational Cancer Control*

Historically, occupational cancer has been known since the 1770's when Sir Percival Pott first reported scrotal cancer among chimney sweeps. It has, perhaps, been rather remarkable that, with the marked increase in industrialization since that time, the number of reported occupational cancers has not likewise markedly increased. That this has not occurred is probably the result of the continual improvement and control of the working environment which has accompanied our industrialization. At one time it may have been a "badge of honor" for the workman to be covered with grease and grime. Today, however, this is becoming increasingly socially unacceptable. In addition, automatic controls have greatly reduced the necessity for another large segment of workmen to come in contact with the materials with which they work. The result has been that it is ever more difficult to distinguish the "workman" from the "office-worker."

Nevertheless, there continue to be groups of workers who must come into rather intimate contact with the materials with which they work. If these materials

are carcinogenic, then a greater or lesser number of these men could, without protection, be expected to develop cancers which would result from their occupation. The medical profession has learned from clinical experience that such occupational cancers may arise in various sites. Table I lists those body areas in which definite occupational cancers have been demonstrated. Although it has been suggested by some that occupational cancer hazards exist in many other occupations, the data are incomplete and insufficient for definite conclusions. The suggestions or allegations should serve as stimuli for continued research until definitive data are obtained.

Perhaps the greatest problem in our quest for knowledge about occupational cancer is the long delay which occurs between exposure to the carcinogen and the development of the cancer. In most occupational diseases, and particularly occupational accidents, the period between the exposure or the accident and the development of a clinically observable result is a matter of a few seconds to a few months. In such cases, the association between the effect and the cause is almost self-evident. In occupational cancer, however, there may be a lapse of ten, twenty, or more years between the exposure and the cancer. This, of course, makes it very difficult to recognize the causes of the cancer.

*Synthesized from conferences among Ralph F. Schneider, M.D., Medical Director, Standard Oil Company (New Jersey); Leo J. Wade, M.D., Medical Director, Esso Standard Oil Company; and Robert E. Eckardt, M.D., Ph.D., Director Medical Research Division, Esso Research and Engineering Company, Linden, New Jersey.

since in the ten or twenty years workers may have been exposed to many different materials.

As an extension of this problem, we are faced with the fact that cancer has a so-called "normal" incidence, and it is only when this "normal" incidence is significantly exceeded in a given occupation that it is possible to say that an occupational hazard exists. Thus, it becomes self-evident that the accumulation of up-to-date, accurate statistics on "normal" cancer incidence is extremely important in occupational cancer research, in order that a base-line for comparison of cancer incidence in specific occupations is available. Such figures can be accumulated by the statistical sections of the American Cancer Society, public health services, industry, and other organizations such as insurance companies.

Perhaps the most exciting aspect of occupational cancer is the fact that once the nature of the carcinogenic materials is understood, and the nature of the exposure has been learned, it should be possible to develop ways of eliminating or minimizing the exposures and thus preventing the cancers. The approach developed by Standard Oil Company (New Jersey) and its affiliates to the problem, would probably interest others concerned with the development of programs to prevent occupational cancer. It is not, of course, suggested that this represents the only, or even an ideal, approach, but is described as an approach which has been found practical.

In 1943, shortly after Esso Research and Engineering Company, the research affiliate of Standard Oil Company (New Jersey), had developed a new cracking process which provided the much needed aviation gasoline for our war effort, one of the chemical engineers of that Company was examining the by-product of this process. He was looking particularly at the heavy by-products which boil above 700°F, a type of material which may go into heavy industrial fuels, but is not found in gasoline service stations. A chemical analysis of these fractions revealed the presence of aromatics which

structurally resembled some of the known carcinogens. He asked himself if these materials, too, might be carcinogenic. Not knowing the answer, he brought his question to the Company's Medical Department. Since the medical staff, likewise, did not have the answer, arrangements were made to have the substances in question tested at Sloan-Kettering Institute for Cancer Research, under the supervision of Drs. C. P. Rhoads and K. Sugiura. The samples, selected by the Company investigators, were painted on the skin of mice, rats, guinea pigs, rabbits, and monkeys. Rats and guinea pigs showed no response, but mice developed tumors and cancers, and rabbits and monkeys more slowly developed tumors.

It was then decided to embark on an extensive testing program, using mice as the test animals. This work was carried out over the course of five or six years, from 1946-1951, the work after 1948 being performed by the Institute of Industrial Medicine of New York University, under the direction of Drs. Norton Nelson and William Smith. In brief, the results showed that those fractions subjected to, or resulting from, the new cracking process and which had boiling points above 700°F, were carcinogenic to the mouse skin. Further, the studies showed that:

1. Dilution in certain degrees could reduce the concentration of carcinogenic materials to levels believed safe.
2. Soap and water washing essentially eliminated carcinogenicity.
3. "Protective" creams provided little, if any, protection.
4. Various processes, some commercially feasible and some not, could influence the carcinogenicity of the fractions.

Having thus determined that a certain fraction of the oil was carcinogenic to mice, the Company took the position that it would be prudent to consider this fraction as potentially carcinogenic to man too, at least until more data were accumulated. As a result, surveys were undertaken to discover how, where, and when men came in contact with this fraction. These

surveys suggested that with the practices then in effect, it was possible for a considerable number of men to have contact with this oil with a frequency that might be undesirable. Therefore, until further information could be obtained on the true extent of the hazard, it was decided to take steps to eliminate contact with these fractions wherever possible or minimize such contact where complete elimination was not possible. The steps taken within the refineries are outlined below:

1. Employees were acquainted with the program being initiated and the reasons for it, in order that their cooperation could be obtained.
2. Good housekeeping was encouraged so that leaks would be stopped and spills cleaned up as soon as possible, in order that none of the oil would be lying around for employees to contact unsuspectingly.
3. Pipes and units containing this fraction were identified in a variety of ways so that employees could readily recognize the need for protective equipment if they had to work on these units.
4. Protective equipment, such as gloves, aprons, rubber suits, boots, etc., was provided for men who had to work on these pipes and units.
5. Pipes and units were flushed out with non-carcinogenic oils and steam whenever possible before men were permitted to work on them.
6. Where contact could not be avoided, men were instructed to wash with soap and water as soon as they could after the job involving contact.
7. In jobs where soiling of the workers' clothing is inevitable, such as tank cleaning, men were provided with clean underwear daily and required to take a shower before going home.
8. Wherever possible, within the refinery, the flow of the fraction in question was restricted.

In addition to these steps and in accordance with good industrial medical principles, men who might be exposed to this fraction in their work were scheduled for detailed inspection of the skin at the

time of periodic medical examinations. This was arranged so that if a problem did develop and someone did develop cancer, it would become known early enough so that treatment could be obtained promptly and indicated additional preventive measures be put into effect.

Many men potentially exposed to these oils have now been followed for periods of as long as thirteen or fourteen years, and it is gratifying to be able to report that not a single case of cancer, attributable to exposure to this fraction of oil, has been discovered. This may mean one of three things: the fraction, although carcinogenic to mice, is not carcinogenic to men; the exposure period has not yet been long enough; or the preventive program has been effective.

The above described approach serves, however, to outline what seems to be a reasonable program for the prevention or the earliest possible recognition of one variety of cancer in industry. In more general terms, any such program consists of five steps, as follows:

1. Review the materials to which workers are exposed to see if any might be carcinogenic.
2. Arrange for animal testing to see if any suspected materials do have carcinogenic activity in animals.
3. If animal testing reveals carcinogens, review the exposures of workers in order to understand how, when, and where they are exposed.
4. Devise means of eliminating or minimizing the exposures.
5. Arrange for medical supervision of the men exposed.

It can be seen that such a program requires the cooperative efforts of chemists, biologists, industrial hygienists, chemical engineers, industrial physicians, and biostatisticians. In addition, it requires the enthusiastic support of management. When all these elements have been obtained in proper and harmonious proportions, it is believed that real progress in industrial cancer prevention can be expected with confidence.

TABLE I
Clinically Established Occupational Cancers

Skin, including the scrotum	Bladder
Coal tar	β -naphthylamine
Coal soot	Benzidine
Shale oil lubricants	
Certain cutting oils	Nasal Sinuses
Crude petroleum waxes	Unidentified agent in nickel refining industry
Ultraviolet light	Unidentified agent in isopropyl alcohol manufacture
Roentgen rays	
Lungs	Bone
Unidentified agent in chromate manufacturing industry	Radium

The First Cancer Research

On December 8, 1773, Bernard Peyrilhe was awarded the Pouteau 1200-livre prize of the Académie des Sciences, Arts et Belles-Lettres de Lyon for his dissertation *De Cancro* describing his attempt to determine the nature of cancer by the experimental method.

The original Latin text bore the appropriate device, "*Prolem sine matre creatam*," from Ovid's *Metamorphoses* II, 553—the same motto, "*Enfant né sans mère*," used thirty years earlier by Montesquieu for his *L'Esprit des Loix*, to indicate that he had no model to follow.

"3rd Observation: Here I will report an experiment, which is particularly interesting to me, concerning the contagion of the cancerous virus. I took about two drachms of virus expressed from a cancerous (human) breast and, having made a wound on the back of a dog, injected it with a syringe, as completely as possible, into the cellular tissue around the wound. I then closed the wound as well as I could with adhesive plaster and bandage. Three days later I removed the dressings. Retraction of the skin revealed a foul-smelling, violet-black ulcer surrounded by emphysema and edema. I closed the wound with the same dressing and inspected it for the second time forty-eight hours later. The symptoms were then acute. The entire skin from head to tail was distended with an edematous emphysema. Blackish ichorous pus oozed from the wound. The poor animal's eyes were bright and his thirst intense. He howled and yelped. Finally my servant, disgusted by the stench of her guest whose piercing cries continued, threw into the latrine this animal whose wound was so precious to me, and thus denied me the opportunity of observing the subsequent course of this factitious disease.

"I made every effort to prove the identity of the cancerous virus and the putrid ichor. I have not omitted or dissimulated any experiment or observation contrary to my opinion. Even though I may not have removed all doubt, I believe I have established at least the probability."

Elsewhere in his dissertation Peyrilhe makes a bid for early detection: "Cancer of the first degree is capable of resolution and very often this occurs by art or by nature."



DOCTORS' DILEMMAS

Q A 67-year-old farmer came to my office last week, complaining of skin growths, gradually increasing in size, on the dorsal aspect of both hands. Examination reveals five lesions on the right hand and six on the left—the lesions vary in size from 0.5 cm. to 1 cm. and present themselves as freely movable excrescences, some of which are centrally umbilicated. What would you suggest in the way of a diagnostic work-up?

A These lesions may represent early carcinoma of the skin or they might be seborrheic keratoses. Both lesions are not too uncommon following prolonged exposure to the rays of the sun. This would be an occupational hazard expected of the farmer. A wide local excision should be performed on each of the described lesions and care should be taken to evaluate the clinical status of the axillary nodes. Of course, further therapy would depend upon the histological findings. The patient, however, should be advised to avoid further exposure to ultraviolet rays.

Q A 39-year-old white woman has noted scaling and itching of the left nipple for one week. Examination reveals superficial pearly-white skin change within the areolar margin. The altered area measures $2\frac{1}{2}$ to 3 cm. The breast itself presents no underlying mass and there is no evidence of nipple discharge or axillary adenopathy. How should such a case be managed?

A The description might suggest the possibility of either eczema or Paget's disease of the nipple. The simplest method of establishing a diagnosis would be the performance of a wedge biopsy of the involved segment of the areola. If a report of Paget's disease is obtained, the patient should be subjected to a radical mastectomy. However, if a diagnosis of inflammation can be proved, local therapy with bland ointments might be sufficient. The only truly important factor in a case such as this is the avoidance of unnecessary delay in establishing a definite histologic diagnosis.

Q I have just done a radical mastectomy on a 31-year-old woman who had a 1-cm. infiltrating duct carcinoma in the upper, outer quadrant of the left breast. The excised axillary nodes show no evidence of metastatic disease. Can I expect a poor prognosis in this patient because of her age?

A Most authorities in the field of breast cancer currently believe that age itself has little influence on the prognosis of adequately treated breast cancer. The status of the lymph nodes (i.e., the extent of the disease), the malignant potential of the tumor, and the host resistance factors probably play a greater part in determining the ultimate outcome. The consensus is that your patient will most likely do just as well as a patient in an older age group who has the same clinical setting.

Q *A 47-year-old white woman, gravida 2, para 2, presents a history of a bleeding left nipple for one week. Pressure applied to the 6 o'clock axis of the left areolar margin produced dark-red material from the central portion of the nipple. There are no other significant breast findings. Cytologic examination of the nipple discharge shows no malignant cells. What therapy do you recommend?*

A Cytologic examination of breast secretion is still in an experimental phase and most surgeons would not rely completely on this technique for definitive diagnosis in a patient such as the one you describe. An excision of the subareolar duct system should be done so that a histologic diagnosis might be obtained. The breast lesion could be an intraductal papilloma or a papillary carcinoma. Additional surgery, of course, would depend on the microscopic appearance of the lesion.

Q *Last week I saw a 28-year-old man who had had a brown skin lesion cauterized by his physician two months ago. The patient became concerned when an area of recurrent pigmentation appeared at the site of cauterization a short while later. Examination reveals a 1-cm., irregular scar on the dorsal aspect of the forearm with a centrally located 2-mm, brownish-black area of pigmentation. How should this case be treated from this point on?*

A The previous cauterization is somewhat unfortunate since there are no data available on the microscopic appearance of the original lesion. Initially this might have been a benign nevus or a malignant melanoma. The latter seems a likely possibility in view of the recurrent pigmentation. A wide excision should be performed, perhaps considering a skin graft to cover the local defect. If a diagnosis of melanoma is obtained, the surgeon must decide the question of regional axillary lymph-node dissection, either separate or continuous with the local operative site.

Q *A 16-year-old high school boy came to my office because of a swelling on the dorsum of the right foot. Clinically this resembles a simple ganglion. Is there any danger in merely observing this mass for a change in size or character?*


A Yes, such a danger definitely exists. Although ganglion of the wrist is not uncommon, it is more unusual to find a ganglion on the dorsum of the foot. Surgical removal should be advised without unnecessary delay to rule out the possibility of synoviomia—a highly malignant soft-tissue tumor.

Q *I recently examined a 33-year-old woman who discovered a mass on the hard palate one month ago. Oral examination reveals a 3-cm., stony-hard prominence in the mid-portion of the hard palate with no abnormality of the overlying mucosa. What would you consider in the differential diagnosis?*

A The description of the lesion suggests a *taurus palatinus*—a benign bony protrusion of the hard palate. Another possibility would be a minor salivary gland tumor which is not uncommonly found in this location. The question of advisability of biopsy should be referred to a head and neck specialist who would be more thoroughly acquainted with both of these two conditions.

Q *A 43-year-old white man with non-resectable bronchogenic carcinoma has received the maximum dosage of radiation therapy. The patient is rapidly approaching a terminal stage because of mediastinal compression and dyspnea. Is any additional therapy indicated or recommended?*

A Such a patient might receive temporary palliation via the administration of HN2 intravenously in doses of 0.1 to 0.2 mg. per Kg. body weight. At times, the improvement is truly dramatic and the palliation afforded may be well worth the effort.



new developments in cancer

Mouse Melanoma . . .

Dr. J. Murray Luck of Stanford University has tested pD2p, a nitrogen mustard derivative containing phenylalanine, against a mouse melanoma and found that it had some carcinostatic power. If the highly toxic drug was administered shortly after melanoma was transplanted it slowed down melanoma development. Three weeks later, the melanoma in treated animals was only 4 per cent the size of melanoma in untreated controls. The finding may be of academic, rather than clinical, significance. This drug was designed to interfere with melanin synthesis; and it has been argued that blocking melanin synthesis would not interfere with melanoma development. These results resurrect the question.

Leukemia Antigens . . .

Bernard Kalfayan of Beekman-Downtown Hospital, New York, has produced rabbit antiserum that completely destroys human leukemic cells in vitro. The findings indicate, however, that it would be dangerous and ineffective to treat human leukemics with the antiserum. Its action against normal white cells—badly needed by leukemia patients—is unpredictable. Kalfayan injected rabbits intraperitoneally three or four times at weekly intervals, and a week or so after the last injection

he bled the animals and separated the antibody-loaded serum. When white cells from leukemic patients and complement were added to the serum, the action was almost explosive—leukemia cells shrank, wrinkled, thickened within minutes, and a half hour later most of them were dead and disintegrating. Normal white cells were much less affected. The antibodies produced in these experiments were of a multiple nature—some seemed specific for leukemic-cell particles, while others attacked particles common to both normal and abnormal white cells.

Radiation "After-Effect" . . .

Scientists at Washington State College have found that storage appreciably increases cell damage from irradiation. The degree of ultimate postirradiation effects depends in part on the storage environment. Jack D. Adams, R. A. Nilan, and Helga M. Gunthardt have demonstrated that postirradiation storage of barley seeds in oxygen over a period of several weeks progressively enhanced radiation effects, while nitrogen decreased them. The gases alone did not induce damage—chromosome aberrations, genetic mutations, reduced viability, shortened seedlings, germination, or field emergence. Earlier Caldecott and Smith found that the immediate application of heat also modifies radiation effects.

Forced Feeding In Cachexia . . .

Drs. A. Raymond Terepka and Christine Waterhouse of the University of Rochester have force-fed nine volunteer patients wasting away from cancer. Some were fed through stomach tubes. Diets were designed to overcome weight loss. All nine patients now are dead. A few seemed to have been helped transiently. None could take it for long. Almost all gained weight while on the diet—some averaged two pounds a day. Much of the gain was due to fluid accumulation, and all gains were lost when feeding stopped. Nitrogen, retained during the diet, was dissipated rapidly off the diet. Four of five of the patients looked and felt better during the experiment; the rest did not.

"Almost a Cancer Cure" . . .

Some drugs knock out all but a few cancer cells. The resistant cells repopulate the body and kill the host. Work by Gerald A. LePage and others (U. of Wis.) suggests how at least some of the drugs work, how they almost succeed, and why, in humans, they invariably fail to cure the cancers. The investigators fed radioactive azaserine and 6-mercaptopurine to cultured normal and cancer tissues. In very small doses, azaserine inhibited to 90 per cent the rapidly metabolizing cancer's use of glycine, a nucleic acid precursor. It took large doses to affect the normal cells' production of nucleic acids. 6-MP also inhibited cancer's nucleic acid production without appreciably affecting normal cells. Cancer cells that survived the poisons eventually devised a new method of making nucleic acids and in this way became resistant to drugs. Nucleic acid components are obtained by cells in two ways: (1) whole, in the diet; and (2) as raw materials which cells must reshape into nucleic acids. Growing normal cells usually use the second method. Cancer cells will use either method, and, when poisoned precursors are fed them, smart survivors will accept only ready-made nucleic acids in the diet.

Sulfur Mustard . . .

A new sulfa mustard appears promising against Hodgkin's disease and other lymphatic cancers treated in preliminary trials at the University of California. In tests on animals and twenty-seven humans, the drug, called SM-1, appeared to be less toxic, longer acting, and more easily administered than nitrogen mustard. It could be administered with safety in the out-patient clinic. When it was given intravenously, SM-1 frequently brought about reduction in tumor masses, lymph-node size, and spleens. At first glance, it seems to have afforded some benefit to a few patients with lung cancer. Sulfur mustard was a World War I poison gas, and this drug is a derivative of it. The work was done by N. L. Petrakis, David A. Wood, S. M. Farber, and A. V. Costantini.

Trauma and Cancer . . .

Another step has been taken in the age-old controversy as to whether trauma plays a role in carcinogenesis. Howard L. Richardson and John B. Thiersch (Institute of Biological Research and U. of Wash.) have produced new evidence that trauma may act as a cocarcinogen. The Seattle investigators fed rats 2-acetylaminofluorene (AAF), which, when fed regularly, induces hepatomas. In the doses used, it had no apparent effect on the digestive tract. When they fed AAF and gave the rats four doses of 1 or 2 cc. of alcohol at two-week intervals, the animals developed a series of stomach conditions, including gastritis, ulcers, hemorrhage, and, in the two rats that were not sacrificed for nine months, cancer of the glandular portion of the stomach. The forestomach was unaffected. The cancers were highly malignant—metastasizing to lymph nodes and liver. In earlier work, Richardson sped the onset of liver cancer by needle-pricking the livers of rats fed butter yellow. Hepatomas appeared at the site of the needle puncture in much less than one-half the time required to produce hepatomas in these rats by butter yellow alone.

Folic Acid Antagonists: The life of leukemic mice was extended -- and in some instances saved -- with folic acid antagonists, with or without delayed administration of citrovorum factor, in experiments at the National Cancer Institute. Moreover, leukemic cells from mice succumbing to the disease showed no resistance to the drugs, even though there had been extensive chemotherapy. The authors -- Goldin, Venditti, Humphreys, Dennis and Mantel -- have considered the possibility that host-resistance factors may be important in death by tumor and death by toxicity.

Cancer Prophylaxis: The cancer seems localized. Nearby nodes are "clean." The surgery is radical and apparently complete. And everyone concerned is optimistic. But one or two years later there is a recurrence. The patient is hopelessly peppered with metastases. What happened? There is a growing suspicion that, despite the thoroughness of the operation, a few cancer "crumbs" may have been overlooked by the surgeon, and that these reconstituted the cancers at distant sites. It is well known that early tumors -- particularly in-situ carcinoma -- exfoliate very readily.

Dr. Warren H. Cole (U. of Ill., immediate past President of the American College of Surgeons) more than a year ago decided that recurrence very easily could be due to exfoliated cells. The Cole and other groups had shown, in animal operations simulating surgical removal of a human tumor, that cells do escape and they do bring about recurrence of the disease. Cole cited the observation of other surgeons and pathologists: One had washed 100 human surgical wounds after operation and found cancer cells in 43 and suspicious cells in 19 others; another found cancer cells in veins draining the operative area in 66 of 107 patients so studied -- they were in the general bloodstream of 78 per cent of the moderately advanced and 100 per cent of the far advanced cancer patients. Cole decided the time had come to evaluate and eliminate the danger. First began the tests of prophylaxis -- on rats. Cole and his associates injected from 110,000 to 220,000 cancer cells into the portal veins of rats. One-half the animals were treated with various dosages of nitrogen mustard, thioTEPA, and other anti-cancer drugs. The rest were untreated controls. In one series the treated animals showed only 7.1, 17.8, and 16.2 per cent cancers; their untreated mates registered 90, 92.1, and 92.3 per cent cancer. The tests showed that to be effective the drug should be freshly prepared

before use and that injections should start soon after inoculation with cancer cells. Drugs given 48 hours after inoculation were ineffective. The first cautious tests were made on patients. No bad side effects were encountered. When 43 had been treated and found to tolerate the drug well, long-term studies leading to eventual evaluation of the procedure were begun. Every other patient with cancer of the breast, rectum, colon, or stomach is given prophylactic treatment -- alternates serve as controls. These four sites were selected because they are drained by veins as well as lymphatics. Very elderly and debilitated patients are excluded. Dr. Cole's group in surgery now take these precautions with test patients: 1) tying off all vessels serving the operative site and, at the end of the operation, administering intraperitoneally a drug to kill any stray cancer cells; and 2) on each of three days following surgery administering the drug intravenously.

Many Bullets, Little Magic . . .

The New York Academy of Sciences and the Cancer Chemotherapy National Service Center brought together the cream of cancer chemotherapists at New York's Barbizon Plaza, March 28-30. Subject of the Conference: Comparative Clinical and Biological Effects of Alkylating Agents.

While nothing of a startling nature developed, the conference served as an excellent summary of the present status of cancer chemotherapy.

The enormous contributions to chemotherapy by Haddow and his Chester Beatty Research Institute, Royal Cancer Hospital, were in evidence throughout the proceedings. Haddow brought ten of his group from London to the conference.

Here is a rundown on some of the major papers:

Price (University of Pennsylvania): Alkylation is the conversion of $H - X \rightarrow R - Y$.

Ross (Chester Beatty): Alkylating agents include sulfur and nitrogen mustards, ethyleneimines, epoxides, methanesulfonates and betalactones. Alkylation involves a positively charged center (carbonium ion of organic or inorganic anions, amino and sulfhydryl groups) reacting with electron-rich groups of biological systems.

(Continued in July Newsletter.)

COMING MEDICAL MEETINGS

Date 1957	Meeting	City
May 30-31	American Geriatrics Society	New York City
May 30- June 1	American Radium Society	Quebec, P.Q.
May 30- June 1	The Endocrine Society	New York City
May 30- June 2	American Therapeutic Society	New York City
May 30- June 2	American Medical Women's Association	New York City
June 1-2	Society for Investigative Dermatology	New York City
June 3-7	American Medical Association	New York City
June 4-6	International Therapeutic Congress	Utrecht, Netherlands
June 17-21	Canadian Medical Association	Edmonton, Alberta
July 1-6	International Congress on Occupational Health	Helsinki, Finland
July 9-11	International Society of Geographical Pathology	Paris
July 14-19	International Gerontological Congress	Merano-Bolzano, Italy
July 15-19	British Medical Association	Newcastle upon Tyne, England
July 15-20	International Congress of Clinical Pathology	Brussels
July 24-29	International Congress of Nutrition	Paris
July 31- Aug. 6	International Congress of Dermatology	Stockholm
Aug. 26-30	Gordon Research Conferences; Cancer Conference	New London, N. H.
Aug. 26-31	Congress of the European Society of Haematology	Copenhagen
Aug. 28- Sept. 3	Congress of International Society for Cell Biology	St. Andrews, Fife, Scotland
Sept. 9-20	International Conference on Radio- Isotopes in Scientific Research	Paris
Sept. 29- Oct. 5	World Medical Association	Istanbul
Oct. 1-4	American Roentgen Ray Society	Washington, D. C.
Oct. 13-18	American College of Surgeons	Atlantic City
Nov. 11-15	American Public Health Association	Cleveland, Ohio

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